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THE OVARY IN ENDOMETRIAL CARCINOMA

With Notes on the Morphological History of the Aging Ovary

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IN 1941, one of us (G. Van S. S.),[1] in a study of 307 consecutive cases of carcinoma of the endometrium, noted that in 156 (87 per cent) of 180 menopausal cases, there was a stromal hyperplasia of the ovaries. In 1942, another of our group (L. C. J.),[2] then at the Free Hospital for Women, amplified that observation and gave a preliminary report before the New England Pathological Society. This finding aroused considerable interest and initiated a study of the aging ovary in general. A note on this subject was made by one of the writers (A. T. H.).[3] The earliest appearance of stromal hyperplasia was seen in the 45 to 49 year age group. After the age of 50 years it was seen with greatest frequency in cases with continued endometrial activity or outright malignancy. On the basis of these observations the present study was undertaken (1) to learn the stromal changes in the ovary from neonatal infancy to old age; (2) to study the ovaries in cases of carcinoma of the endometrium; (3) to compare these with a control group.

Review of Literature

The Ovarian Stroma Before the Menopause.—The normal sequences of the stromal cell are at present considered to be as follows (Fischel,[4] Kingsbury,[5] Corner[6]): in the embryo the local mesenchyme gives rise to the stromal cell which in postnatal life is modified to become the cell of the granulosa, theca interna, corpus luteum, and finally the corpus albicans. For the purposes of this paper we wish to emphasize the following features of the above enumerated sequences. The spindle-shaped stromal cell gradually grows larger, becomes cuboid, shows accumulation of anisotropic fat, and then in retrogression degenerates and is replaced with scar tissue.

The stromal cell has thus a multipotentiality of form and probably function which normally follows an orderly sequence. Hisaw,[7] in his review of the

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physiologic basis for the development of the Graafian follicles and ovulation, suggests that the ovum, or a "system of self-contained organizers," may have a guiding influence in this process. This concept of ovarian stromal cell multipotentiality is in accord with the view of the totipotentiality of the mesenchyma in the urogenital ridge (Schiller,[8] Gruenwald[9]). In connection with the multiplicity of function, interesting histochemical evidence is advanced by Dempsey and Bassett.[10] They found that the cells of the theca interna and corpus luteum contained sterols, while the granulosa cells did not.

The Interstitial Cells of the Ovary.—In 1865 His[11] described aggregates of lipid-laden epithelioid cells in the ovaries of cats. In 1901 and 1902 Limon[12] and Bouin[13] considered these as endocrine gland-cells and proposed the term "interstitial gland of the ovary." Other investigators, notably Wallart,[14] agreed with these observations and in 1907 the latter author, studying human material, found the incidence of interstitial cells to be highest at puberty. Kingsbury,[5] in 1914, thoroughly reviewed the subject and studied the problem in the ovary of the cat. In 1919 Corner,[6] investigating the development of the corpus luteum in the sow, made observations on the ovarian stroma in this animal as well. It is now generally held that the interstitial cells are remnants of granulosa from atretic follicles and that subsequent contraction of the scar may displace the cells well away from the original site. Kingsbury[5] was of the opinion that there is no morphologic or physiologic support for the idea of an interstitial gland of the ovary per se.

Recent knowledge about the structure and hormonal effects of the granulosa and theca cell tumors (Novak,[15] Dockerty[16]) supports, in our opinion, the original views of Limon, Bouin, and Wallart, at least as to the hormonal potentiality of the interstitial cells. Several points of caution in the study of this problem are in order. In the past, most of the material used was from animals in the very young or fertile period of life. Very little human material was examined and the knowledge of the senile ovary, in particular, is very scant. True, it is important to distinguish the interstitial cells from aggregates of granulosa cells which only on serial section can be shown to be part of a maturing or atretic follicle. Similarly, in senility, small groups of invaginated germinal epithelium may also simulate interstitial cells. Nevertheless, our study leads to the conclusion that, at least in the senile ovary, the stromal cell is capable of recapitulating the normal sequences of the granulosa, theca interna, corpus luteum, and their neoplastic derivatives without the presence of the primordial ovum. We have seen numerous instances of this process in its various transitional stages, without relation to atretic follicles or their scars.

The Ovary in Endometrial Carcinoma.—Advances in the knowledge of hormonal factors in cancer have been associated with studies on the relation of the granulosa and theca cell tumors to endometrial carcinoma (Novak,[15] Dockerty[16]). The association of endometrial hyperplasia with carcinoma was first investigated by Taylor,[17] and then Herrell,[18] and Novak.[19] The endocrinological aspect of uterine cancer in general is ably reviewed by Dockerty,[16] Block,[20] and Nathanson.[21] Jones and Brewer[22] reported on a study of the uterus and ovaries in 67 cases of fundal cancer. They concluded that there is no relation between ovarian "cysts," endometrial hyperplasia, and endometrial carcinoma. Of the total series, none of the patients was over 51 years of age. There were only five patients in the 45 to 51 year age group. The conclusions are based mainly on the premenopausal group. Corpora lutea are described with an inner fibrous lining, yet no comment is made about the condition of the lutein cells. This lining is seen best in the retrogression stage. In our series there were corpora lutea which we considered definitely abnormal in that while the fibrosis at the inner and outer borders was well advanced, the lutein cells and their capillary

bed were remarkably well preserved and apparently functionally quite active. This subinvolution, and presumable persistence of hormonal stimulation, we consider to be significant. It is of particular interest to us to note that Jones and Brewer speak of a "dense" stroma in their cases, and that a photograph in Herrell's report to illustrate a typical "cystic" ovary encountered frequently in his series shows several dark areas in the stroma.

Materials and Methods

All the cases of endometrial carcinoma from the files of the Free Hospital for Women, in which sections of the uterus and ovaries were available, were used. A small number was excluded because (1) the diagnosis of carcinoma was not clear-cut; (2) the sections were faded; (3) the ovarian architecture was markedly distorted by metastatic or associated primary tumor; (4) the sample chosen (only the wall of a cyst, for example) did not permit valid observations of the ovary. A total of 331 acceptable cases were examined. The tissue was fixed in formaldehyde, 10 per cent, U.S.P. or Bouin's fluid, embedded in celloidin or paraffin, and stained with hematoxylin and eosin. In several instances, the sections were also stained with Mallory's aniline blue, phosphotungstic acid hematoxylin, and Foote's reticulum, counterstained with Van Gieson.

For the control group, an approximately equal number of cases, with the same age distribution, was chosen from the autopsy files of the Peter Bent Brigham Hospital. The same criteria as above were applied. In order to approach the normal as much as possible, preference was given to cases of cerebral hemorrhage, coronary occlusion, fulminating sepsis, or sudden death from other causes. A total of 307 such cases was examined. In none was there clinically appreciable gynecologic disease. The tissue was fixed in Zenker's-acetic acid or formalin, embedded in paraffin, and stained with eosin-methylene blue or hematoxylin-eosin.

To evaluate differences in microscopic appearance due to differences in preparation methods, sections of the ovary from ten cases of endometrial carcinoma, prepared as the rest of the control group, were studied but not included in the tumor series. Although Zenker's-acetic acid fixative does accentuate collagen and produces more nuclear shrinkage than Bouin's fluid, the differences were judged not sufficient to make comparisons unreliable.

In addition, numerous sections from the ovaries of the newborn, infants, children, and adolescents from the autopsy files of the Children's Hospital were prepared with all the above enumerated fixation and staining techniques, except celloidin, and were studied to obtain an understanding of the morphologic history of the ovary, especially its stroma. In this group, too, an attempt was made to choose cases of sudden death, brain tumor, birth injury, etc. In almost all cases, the tumor, control, and study groups, the ovarian sections represented a mid-coronal plane and were, therefore, anatomically comparable.

Results and Analysis

Ovarian Stroma Before the Menopause.—It is generally held that the ovarian stromal cell has the potentiality to act as a fibroblast as seen in the atretic follicle, the corpus albicans, or in ovarian neoplasms such as the fibroma, granulosa, and theca cell tumors. Our observations lead us to conclude that this cell, in its behavior as a connective tissue element and the true fibroblast, are not identical. The morphologic differences are first seen best when the luteinized cells of the theca interna, accompanied by capillaries, and in our opinion fibroblasts as well, penetrate between the clefts of the young corpus luteum. When the latter retrogresses the epithelial elements degenerate but leave behind a very delicate but rich reticulum. It is at first argentaphil and later stains as collagen.

Fibroblasts actively proliferate at the outer margins, the inner border, and between the clefts, but never invade the reticular bed of the degenerated granulosa lutein cells. Ultimately the reticulum is hyalinized into a homogeneous mass of rather special scar tissue. The vascular bed atrophies, the corpus albicans is sharply demarcated from its surrounding structures and, albeit vaguely, retains the outlines of its precursor.

In the formation of an atretic follicle the sequences are essentially similar to those resulting in the corpus albicans, except that there is more fibrous penetration. A band of material similar to the hyalinized reticulum of the corpus albicans, but much narrower, remains. Occasionally a few small round pyknotic cells, possibly remnants of granulosa or theca cells and a few lymphocytes are seen in and around the scar.

It is readily agreed that with ordinary staining methods the individual resting stromal cell is indistinguishable from a fibrocyte, but from the following evidence we conclude that the stromal cell is at least a special type of connective tissue and that it does not produce collagen in the usual sense. (1) The resting stromal cells *en masse* are recognized through most of the life of the ovary by the relative lack of collagen and the presence of delicate intercellular reticular fibrils. These usually have no constant orientation in respect to the axis of the nucleus. Collagen fibers, in contrast, are usually in the direction of the long axis of the nucleus. This is seen best in the Foote's reticulum stain counterstained with Van Gieson. (2) Very early in embryonic life the tunica albuginea is distinguished from the rest of the cortex by an abundance of collagen. In senescence it becomes the main source for fibrosis of the ovarian stroma. (3) A study of the young corpus luteum with reticulum and connective tissue stains makes it possible, we believe, to differentiate the theca lutein cells from the fibroblasts. (4) The formation of a corpus albicans resembles but is not identical with scar tissue formation elsewhere in the body. That the stromal cell is normally in intimate relation with fibrous tissue is not disputed. The remarkably rich capillary network in the cortex with its adventitial fibroblasts makes this point quite clear. The thecoma (Fig. 1) recapitulates and even exaggerates this fundamental pattern very well.

Ovarian Stroma in Senescence and Senility.—The description by Hertig[3] need not be repeated here except to emphasize the stromal changes. In senescence there is a gradual disappearance of the primordial ova, Graafian follicles, maturing or atretic, and follicular cysts. Aside from the "germinal" inclusion type and its derivatives, cysts are extremely rare after 50 years of age. In senility the stromal cell nuclei shrink greatly. Fibrous tissue penetrates the cortical stromal layer from the tunica albuginea as well as from the medulla. The reticular fibrils become hyalinized. Additional collagen is derived from the vascular adventitia. Finally, in advanced old age, the cortex is distinguishable with difficulty from old fibrous tissue elsewhere in the body (Fig. 2). From the age of 40 years on the incidence of germinal inclusion cysts increases. These must be differentiated from the follicular, theca lutein, or corpus luteum types. In the latter at least, the remnants of a theca interna and its vascular wreath can often be recognized. To speak of "cysts" without qualification adds to the confusion. The so-called "simple cyst," as the term is used in this laboratory, is a structure of unknown antecedents. It may be of follicular or germinal epithelial origin, but the lack of definitive epithelium makes it impossible to determine which structure is responsible for cyst formation.

In the senile ovary there is considerable individual variation in the amount of residual stroma and the number and size of corpora albicantia. This is probably, at least in part, a reflection of the individual's past history (frequency of ovulation, atresia of follicles, intra-abdominal, and systemic disease).

Ovarian Stromal Hyperplasia.—The ovary in most cases of endometrial carcinoma has a cortex which is unusually dense and often assumes the shape of spherical or scalloped masses. These do not necessarily bear a relation to the surface gyri. The pattern is reminiscent of miliary intramural leiomyomas of

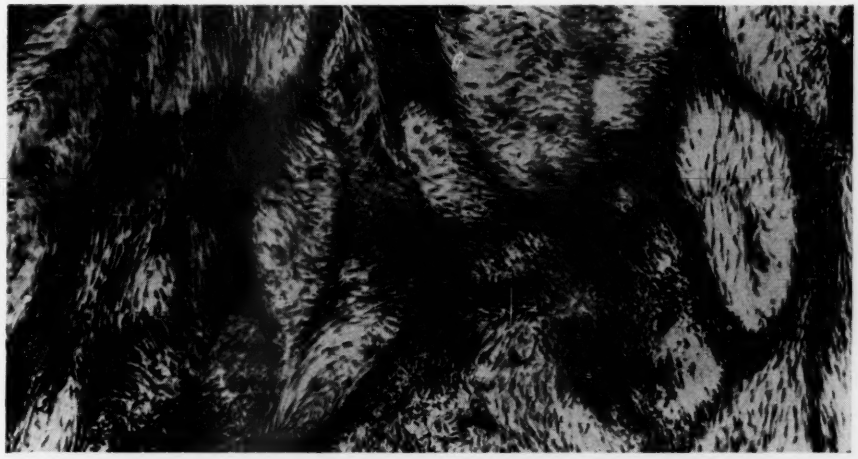

Fig. 1.—Section of thecoma to illustrate fundamental pattern of ovarian stroma. The dark granules of lipid are limited to the ovarian stromal cells. The clear zones, usually around vessels, are free of lipid and contain fibrocytes and collagen. Hematoxylin-Sudan III, ×130.

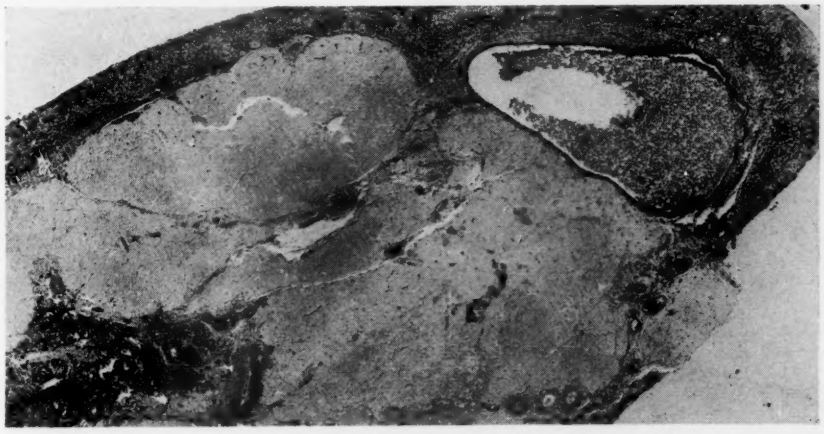

Fig. 2.—A senile ovary from a 69-year-old woman. A germinal epithelium inclusion cyst is also shown. E.M.B., ×30.

the uterus (Figs. 3 to 6). On more detailed examination it is seen that the stromal cells are grouped into more than the usual number of whorls and fascicles (Fig. 8). The nucleus is bluntly oval instead of the usual spindle shape of the resting cell. The nucleus reaches a length of 12 to 15 mu and a width of 6 to 8 mu. The chromatin is disposed at first loosely in a clear ground substance. Subsequently it is gathered into large granules. The reticular fibrils become readily recognizable. Collagen is scant. This accounts for the naked-eye impression that the cortex is unusually dark. It is not due to hyperchromatism of the stromal cell nucleus. The latter, in fact, is lighter on the whole than

the nucleus of the resting stromal cell. This pattern we consider minimal evidence of stromal hyperplasia.

In a smaller number of cases one observes a still greater increase in the width of the nucleus, condensation of the chromatin into coarse granules, and

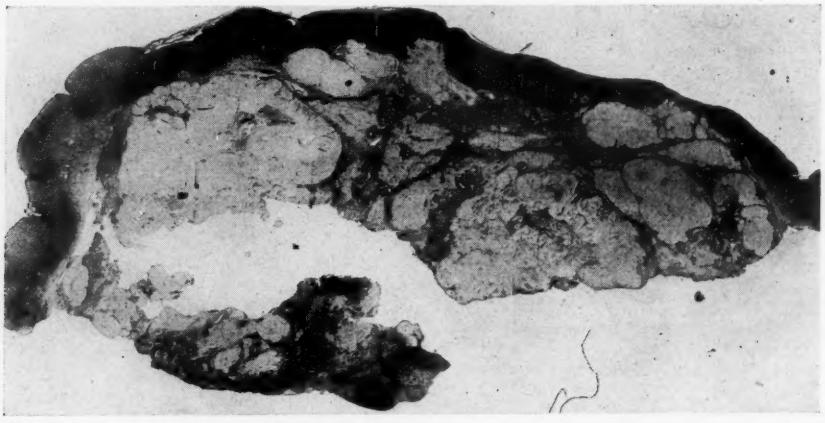

Fig. 3.—The ovary from a 59-year-old woman, showing stromal hyperplasia. Note its nodular character. Hematoxylin and eosin, ×10.

Fig. 4.—Detail of stromal hyperplasia. Note the dark appearance and the condensed connective tissue at the periphery of the nodules. E.M.B., ×30.

occasionally the appearance of small poorly demarcated clear spaces in the ground substance. Many of the cells exhibit a prominent nucleolus seen best in Bouin's fixed tissue. The accompanying capillaries appear more prominent than usual (Fig. 9).

In a still smaller number of instances one sees the above picture plus scattered frankly epithelial lipid-laden cells with a round nucleus 8 to 9 mu

wide containing a prominent nucleolus. The cell margin is distinct. These cells are seen singly or sometimes in groups. Transitional forms between the resting stromal cell and the above are also seen (Fig. 10). These aggregates bear no relation to atretic follicles or their scars. For this appearance we use the term thecomatosis.

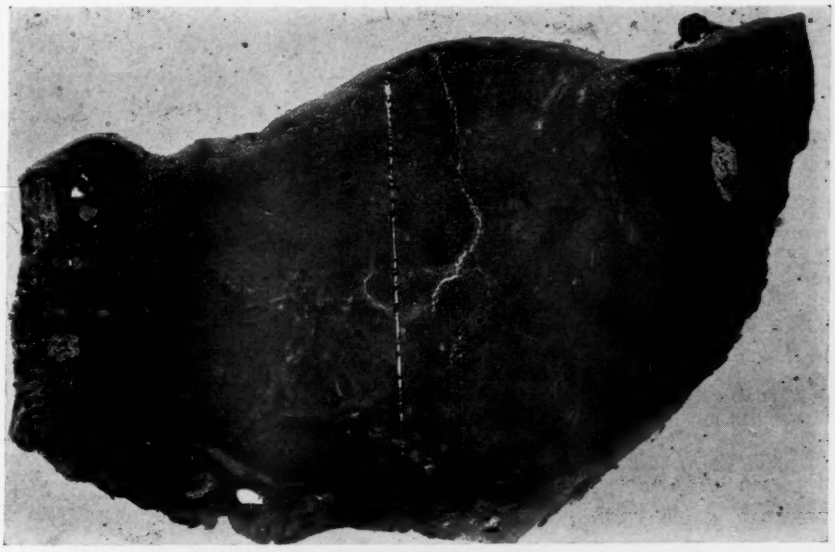

Fig. 5.—A more diffuse variant of stromal hyperplasia. Hematoxylin and Eosin, ×10.

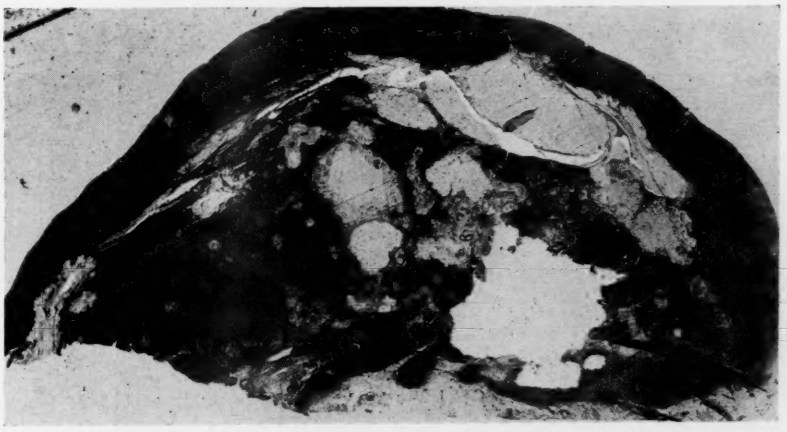

Fig. 6.—Stromal hyperplasia involving part of the medulla (woman, aged 62 years, menopause at 50 years). Hematoxylin and eosin, ×10.

What we believe are retrogressive changes are now to be considered. They are characterized by: (1) a reduction in the size of the nucleus; (2) increase in the amount of true collagen; (3) hyalinization of the reticular fibrils. The nodular character of the stromal hyperplasia is somewhat accentuated by a coarsening of the molded collagen around the periphery. Thus it is possible to recognize evidences of a former hyperplasia (Fig. 12).

In retrogression, at least some of the epithelial cells above described do not revert to the appearance of a resting stromal cell. Instead, there is apparently

a transformation into foreign-body giant cells, or degeneration with giant cell response. This is associated with proliferation of capillaries in the early stage, and the development of intra and extra cellular crystals of anisotropic fat (Figs. 11 to 13). These are the "cortical granulomata" described by Hertig.[3] It is to be emphasized that the history of the patients showing such structures in their ovaries did not give any grounds to believe that these cortical granulomas were the result of foreign bodies introduced surgically or derived from known

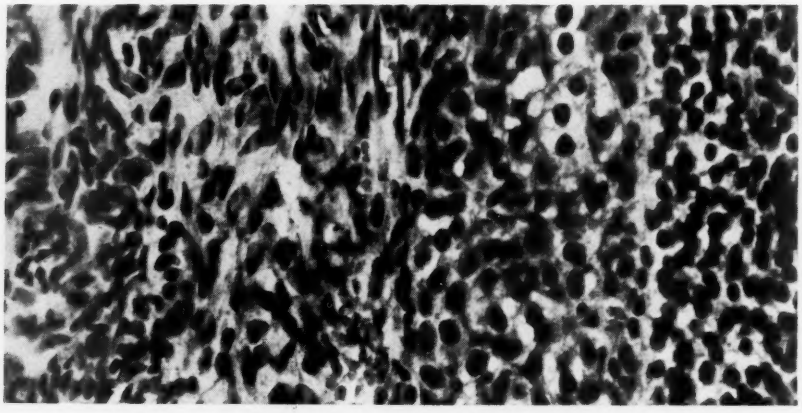

Fig. 7.—Segment of maturing Graafian follicle. The normal sequences of the stromal cell, exclusive of luteinization, are shown. Hematoxylin and eosin, ×540.

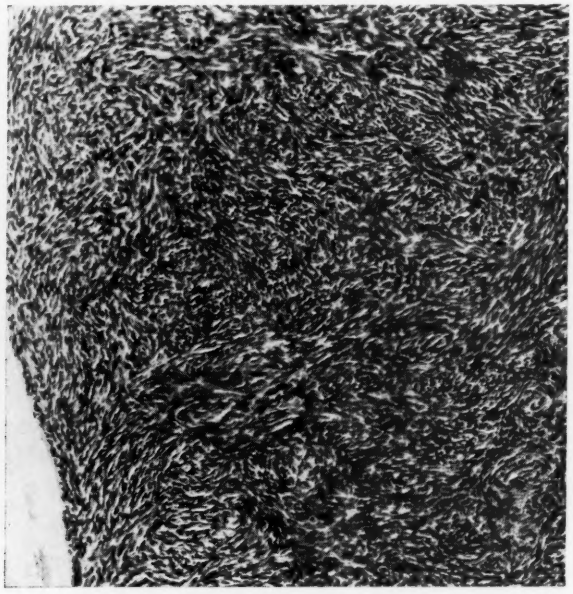

Fig. 8.—Stromal hyperplasia. Note the plumpness of the cells and increase in whorling. Hematoxylin and eosin, ×130.

intraperitoneal disease. We do not know with certainty whether the epithelial cells are transformed into foreign body giant cells or whether the former degenerate and lead to giant cell response. It is of interest in this connection to note

Corner's[6] observation that the lutein cells can transform themselves into macrophages. The above-described stromal changes are, in our opinion, an abnormal recapitulation of the normal sequences of the stromal cell (Fig. 7). All of these, except the cortical granulomas, are seen in the natural history of the follicle, corpus luteum, and corpus albicans.

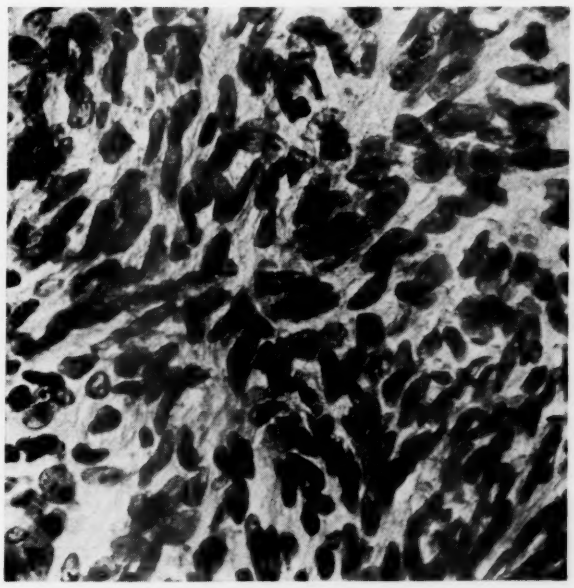

Fig. 9.—A more advanced stage of hyperplasia. Compare with Fig. 7. Hematoxylin and eosin, ×540.

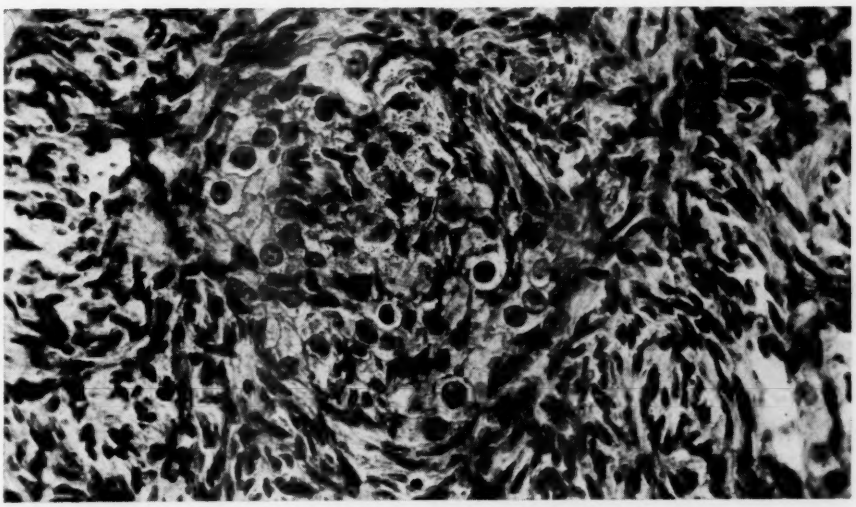

Fig. 10.—Luteinization in stromal hyperplasia. Hematoxylin and eosin, ×540.

As can be seen from Table I, the age range of both carcinoma and control cases was from 30 years to over 70 years. The oldest patient in the carcinoma group was 74 years of age. There was one case of a 26-year-old woman with endometrial malignancy. It was included in the fourth decade group.

Stromal hyperplasia was diagnosed whenever most of the cortex showed the above-described findings. Stromal hyperplasia is a generalized process. Therefore, even a small amount of available cortex in a given section may be sufficient to make the diagnosis. Because this is essentially a quantitative change, there

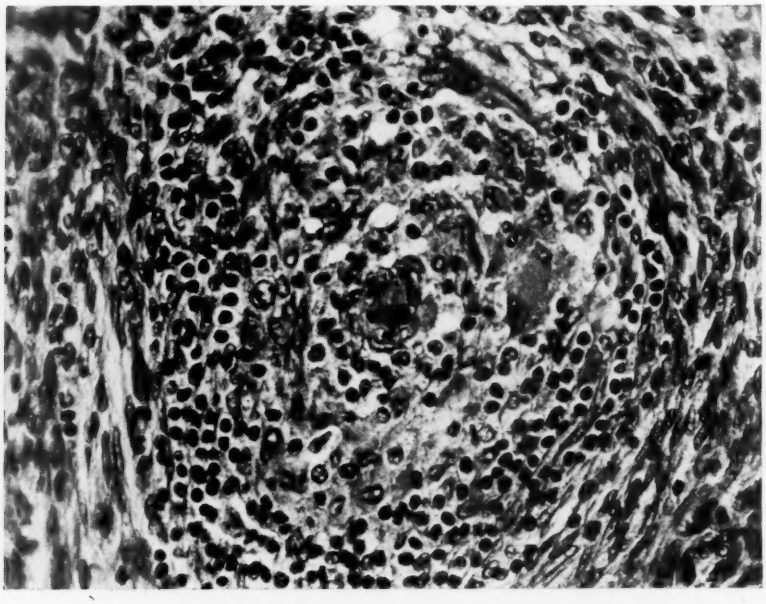

Fig. 11.—Early stage in the formation of a cortical granuloma. Hematoxylin and eosin, ×540.

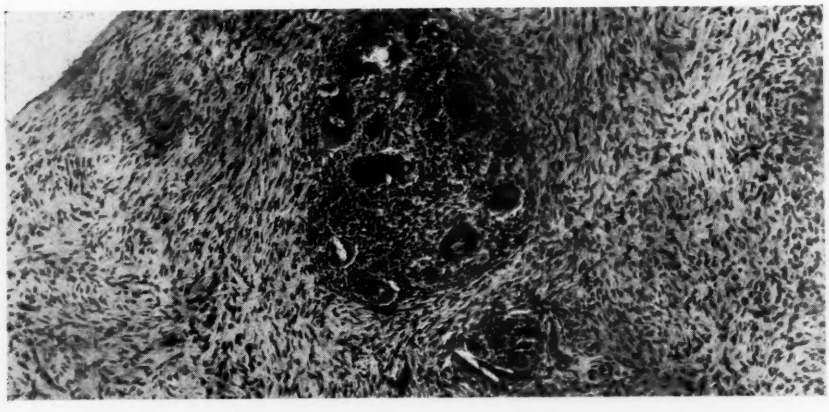

Fig. 12.—Old cortical granuloma. Note the retrogressive changes in the adjacent stroma. Hematoxylin and eosin, ×135.

were not a few instances where a strictly objective decision was quite difficult. Thus the general figures are valid to indicate a trend only. Of some help was the knowledge of the patient's age. An unusually well-preserved ovarian cortex in a woman of 60 years or over weighed heavily in favor of hyperplasia, while in the woman of 35 years or less, the same appearance was not significant, unless other signs of hyperplasia were found.

TABLE I. STROMAL HYPERPLASIA OF THE OVARIES IN CASES OF CARCINOMA OF THE ENDOMETRIUM AND IN CONTROLS

AGE (YEARS)	CASES—TOTAL		STROMAL HYPERPLASIA			
	CONTROL	CARCINOMA	CONTROL	PER CENT	CARCINOMA	PER CENT
30 to 39	11	9*	4	36	5	56
40 to 49	60	57	25	42	45	80
50 to 59	105	140	45	43	116	83
60 to 69	109	113	54	40	100	88
70+	22	12	8	36	11	92
Total	307	331	136	44	277	84

*Includes one case of a 26-year-old woman.

Fig. 13.—Identical area as in Fig. 12. Photographed with polarized light to illustrate the crystals.

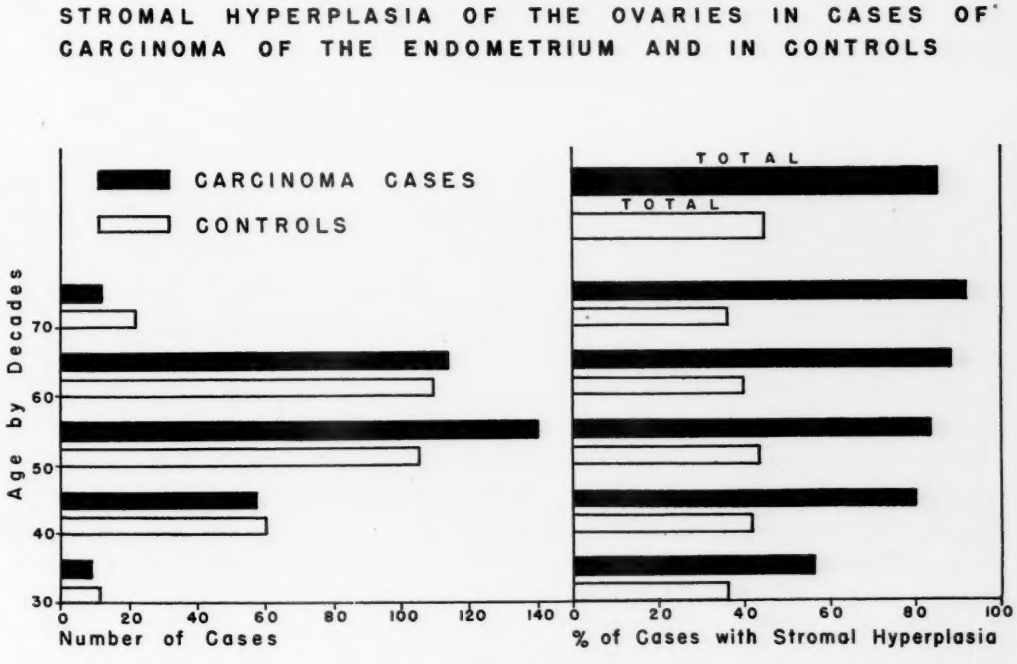

Fig. 14.

A problem arose in the cases where radiation therapy was given before hysterectomy. Only in a few such was there a characteristic effect on the ovarian vessels and stroma. In most, the ovary appeared to be well preserved and showed the various changes with the same frequency as the nonradiated cases. It was decided, therefore, to include the total group of 34 in the general category and apply the same criteria of stromal hyperplasia.

From Table I it is also seen that stromal hyperplasia is present in 36 to 43 per cent of the controls. It reaches its height in the fifth decade, and then tends to subside both in incidence and degree of activity with advancing age. In the carcinoma series there is a significantly higher and increasing incidence in all decades past 30 years (56 to 92 per cent). It persists well into advanced senility, and retains morphological evidence of vigor. Our study of the premenopausal ovary, based on the daily experience with a large amount of material in a laboratory of gynecologic pathology, and a small sampling study, leads us to conclude that stromal hyperplasia is extremely rare in the woman before the fourth decade and uncommon before the fifth decade.

Cysts—Simple, Follicular, Theca, and Corpus Luteum.—From Table II it is seen that there is a significantly higher incidence of such cysts in the fifth and sixth decades in the carcinoma series. For the total it is over twice as common as in the control group. An impressively large number of these cysts in the tumor group are of the subinvoluted theca or corpus luteum types. A question poses itself. Are such cysts a reflection, in the premenopause, of the same stimulus which produces stromal hyperplasia in senility, and is the difference accountable to the presence of primordial ova in the younger group? Herrell[18] is much impressed by the cysts in the ovaries of his carcinoma group. In our study these subinvoluted cysts were considered as corroborative evidence of stromal hyperplasia, although the other criteria were required for a positive diagnosis.

TABLE II. DISTRIBUTION OF OVARIAN STROMAL CELL AND GERMINAL EPITHELIUM DERIVATIVES IN CASES OF ENDOMETRIAL CARCINOMA AND CONTROLS

AGE (YEARS)	CYSTS SIMPLE, FOLLICULAR, THECA LUTEIN CORPUS LUTEUM		CYSTS GERMINAL INCLUSION		CYSTOMAS		CORTICAL GRANULOMA		THECOMATOSIS		THECOMA	
	CONTROL	CARCINOMA	CONTROL	CARCINOMA	CONTROL	CARCINOMA	CONTROL	CARCINOMA	CONTROL	CARCINOMA	CONTROL	CARCINOMA
30 to 39	2	3	–	1	–	–	–	–	–	–	–	–
40 to 49	11	20	8	17	1	3	1	4	–	–	–	2
50 to 59	3	14	17	38	6	6	2	10	2	7	1	6
60 to 69	–	1	22	28	10	11	1	11	1	5	1	8
70+	–	–	7	3	–	–	–	1	–	–	–	2
Total	16	38	54	87	17	20	4	26	3	12	2	18

Germinal Epithelium Inclusion Cysts.—These structures are seen most frequently in the sixth and seventh decades both in the control and carcinoma series. They are more common in the latter group. Their relation to invagination of the germinal epithelium is usually not difficult to demonstrate. On the other hand the degree of stromal activity does not necessarily correspond to the degree of surface convolution. Although we feel that the cysts are related to stromal activity there are probably other factors, as well, which have to do with the formation of surface gyri.

Cystomas.—In this group are included the pseudomucinous, serous, and cystadenofibromatous types. The most common in both series are the pseudomucinous variants. The cystomas are present in essentially the same frequency and age distribution in the controls as in the tumor series.

Cortical Granulomas.—There is a decidedly greater incidence of these in the tumor group. The order of magnitude of their occurrence (7:1), is nearly the same as that of thecomatosis and thecoma. This supports the view that cortical granulomas represent one form of end-result of stromal hyperplasia. It is true that in a few cases the evidence of former hyperplasia is rather poor. It also must be pointed out that recognition of cortical granulomas in Zenker-acetic acid-fixed material requires closer examination and longer search than in Bouin-fixed tissue; therefore the figures on these structures in the control series are not entirely reliable.

Thecomatosis.—There is a decidedly higher incidence (4:1) of this stromal change in the carcinoma group. In several instances the diagnosis of thecoma was hard to avoid. Diffuseness of the process, absence of a capsule, failure of displacement of normal ovarian architecture, all favored the nonneoplastic character of thecomatosis.

Thecoma.—Included in this group was one case of granulosa cell carcinoma with coexistent endometrial carcinoma. All the others had the characteristics of theca cell tumors. Not included were three cases of nonestrogenic fibroma in each of the carcinoma and control series. In these no evidence of probable theca cell origin could be found. As can be seen from Table II, the incidence of thecoma in the carcinoma series is nine times as great as in the controls. It was noted that the opposite ovary, not involved by the theca cell tumor, invariably showed stromal hyperplasia, but not necessarily of a high degree of activity.

Our findings in this respect are in general accord with previous reports (Smith,[23] Novak,[15] Dockerty[16]). In our series the incidence was 5.4 per cent of the carcinoma group, and nine times as frequent as in the controls.

Discussion

During childhood, i.e., between the ages of 5 and 8 years, estrogenic substance is found in small amounts in the urine. Its source is unknown but attributed in good part to the adrenal glands. According to direct evidence in animals and circumstantial evidence in human beings, estrogen stimulates the secretion of luteinizing hormone (LH) by the anterior lobe of the hypophysis and causes its release. Experimentally LH, in combination with amounts of anterior hypophyseal follicle stimulating hormone (FSH), too tiny in themselves to bring on the follicular secretion of estrogen, causes the nonfibroblastic cells of the ovarian stroma to secrete estrogen. The morphologic stromal cell activity at puberty, noted by Wallart,[14] would seem then to be the result of gradually intensified LH ovarian stroma interaction, first preliminary to and then concomitant with cyclic follicular activity. It seems likely that the ovarian stroma contributes to the estrogen secreted by the ovaries until they are exhausted of their follicles, and thereafter is the only source of whatever estrogen they may secrete. The incidence of stromal hyperplasia between the ages of 30 and 40 years and its peak between 50 and 60 years probably is in inverse proportion to the number of extant ova and follicles, and very likely represents a compensatory

effort to respond to hypophyseal stimulation as ova and follicles are depleted. Normally, when the ovaries become senile, the endogenous production of estrogen is so low that no evidence of LH stimulation is detectable, viz., there is insignificant, if any, ovarian stromal activity and, by present methods, essentially pure FSH is the only gonadotropin secreted by the pituitary gland.

From the above considerations it seems reasonable to postulate that LH may be involved when the ovarian stroma behaves abnormally. Conceivably LH, either spontaneously secreted or stimulated by extraovarian factors (e.g., estrogen from the adrenal cortex), might in itself initiate abnormal stromal activity, even the stromal tumors. Regardless of etiology, estrogen-producing ovarian tumors probably call forth LH which in turn may play a part in their continued growth and secretory activity. The known estrogen-producing tumors are, of course, the granulosa cell tumors and thecomas. Taylor and Millan[24] reviewed the literature concerning the association, after the menopause, of tumors other than the granulosa and thecal cell types with endometrial proliferation, and added two instances of their own, both being of the pseudomucinous variety. Smith,[23] on the basis of postmenopausal endometrial proliferation, considers the cystadenofibromas, both serous and pseudomucinous, estrogenic. On the other hand, evidence that postmenopausal ovarian stromal hyperplasia is accompanied by the secretion of estrogen is not yet established,[1] though in its most pronounced development which we have termed thecomatosis, its appearance almost compels the diagnosis of thecoma.

That LH may be stimulated by extraovarian factors is becoming more than a concept. Smith and Smith[25, 26] have collected evidence, and contributed their own, that products of protein catabolism result in pituitary LH activity. They worked with catabolized endometrium as found in fresh menstrual discharge. Pituitary gonadotropic function caused by tissue damage brings to mind the experiments of Brambell, Parkes, and Fielding,[27] in which the ovaries of mice exposed to x-rays were discovered to have stromal hyperplasia and to be secreting estrogen, and also the later investigations of Furth and Butterworth,[28] in which x-radiation actually produced granulosa cell tumors in the ovaries of mice. Since in these studies the whole animal was exposed to x-rays, a chief factor in the accomplishment of the observed results might well have been protein catabolism from tissue damage by the radiation. In human beings the occurrence of granulosa cell tumor has been noted following irradiation.[29, 30] Mild tissue damage might also account for the improved pituitary-ovarian function and the clinical improvement so often brought about by low dosage irradiation of pituitary and ovaries in patients with functional disturbances. In the light of this discussion, the existence of a hormonal factor in endometrial carcinoma will now be considered.

A. Estrogen as an etiological agent.—Estrogen is known to be carcinogenic in susceptible animals—in prolonged unphysiologic dosage. Conceivably, therefore, in the susceptible patient, it may tip the balance of unknowns in favor of endometrial malignancy. Crossen[31] presents figures showing that a delayed menopause, with its prolonged estrogenic activity, is four times more frequent

in those developing endometrial cancer than in controls. That the role of estrogen per se may be a minor one, however, is indicated by (1) the fact that a larger number of women do not get cancer of the endometrium, (2) that this cancer occurs many years after the menopause in patients in whom there has been no known intervening exposure to estrogen, and (3) that it may occur long after castration. Smith[1] reported three instances, 15, 17, and 30 years, respectively, following bilateral oophorectomy.

B. The concomitant condition of the endometrium and ovaries in carcinoma of the endometrium.—A significant, though far from constant association of endometrial proliferation with carcinoma has been found.[1, 17, 18, 19] In the present state of knowledge endometrial proliferation must necessarily be interpreted as reflecting secretion of estrogen by the ovaries. Although some estrogen is excreted after ablation of the ovaries and assumed to be of adrenal origin, it has not been reported as sufficient to cause endometrial proliferation. Herrell[18] was impressed by the cysts in the ovaries of his carcinoma group and, as already stated, the incidence of cysts in patients of our own group between the ages of 40 and 60 years is over twice as great as in the controls, an impressively large number being of the thecal and corpus luteum types. These are the result of FSH-LH stimulation. These, with the cystomata, thecomas, thecomatoses and stromal hyperplasias, add up to well over an 80 per cent incidence of ovarian activity in our series of cases with endometrial carcinoma. How explain the striking association of ovarian activity with endometrial cancer? If the ovarian activity is an etiological factor in endometrial carcinogenesis what causes such activity? A possible answer to the first question is presented in the following paragraph.

Cancer of the endometrium is characterized by bleeding and discharge, both of which are signs of tissue breakdown, protein catabolism. On the basis of the first part of this discussion, the absorption of products of protein catabolism would be expected to stimulate the secretion and release of anterior pituitary LH which, in combination with FSH, would strongly stimulate in the ovaries any cells still capable of responding, thus perhaps accounting for the ovarian and endometrial findings in patients with the disease. In those patients with inactive ovaries and endometrium in the presence of endometrial cancer there could be postulated (1) insufficient absorption of protein breakdown products to give adequate anterior lobe stimulation, or (2) complete absence of cells in the ovaries capable of responding to gonadotropic stimulation. The state of the ovaries in patients with endometrial cancer then might depend on the amount, rate, and duration of absorption of the products of protein catabolism in the uterus, presumably originating for the most part from cancer tissue. As a corollary of this theory, it would be necessary to find some other focus of protein catabolism in those postmenopausal women with active ovaries and without endometrial cancer to account for the initiation of the chain of events resulting in ovarian stimulation and endometrial proliferation, e.g., in ovarian tumors themselves, in tumors elsewhere in the body, in local or systemic areas of infection, from cardiovascular disease, etc. Protein catabolism and pituitary stimulation may have far-reaching ramifications, and conceivably could play a part in hyperplastic changes in the female breast, in prostatic hypertrophy, in various other endocrine and metabolic dysfunctions, even in the etiology of tumors.

Summary

Routine sections of the ovary from 331 cases of carcinoma of the endometrium were studied, and the findings compared with a control group of approximately the same number and age distribution obtained from selected autopsy

material. Sections of the ovary from early infancy to old age obtained at autopsy were also studied with the aid of connective tissue, reticulum and nuclear stains, to determine the changes in the stroma throughout life.

Conclusions

1. The ovarian stroma has the competence to differentiate into the cells of the granulosa, theca interna, corpus luteum, and corpus albicans.

2. This process normally follows an orderly sequence, possibly regulated by the ovum.

3. In senility this differentiation recapitulates the normal sequences, but in disorderly manner, leading to stromal hyperplasia, thecomatosis, cortical granuloma formation, and granulosa and theca cell tumors.

4. Stromal hyperplasia makes its appearance in the early period of senescence (fourth and fifth decades), reaches its height in the sixth decade, and thereafter tends to subside with old age.

5. Stromal hyperplasia is significantly more frequent in cases of endometrial carcinoma (56 to 92 per cent) than in a control group (36 to 43 per cent) and persists into advanced old age.

6. The thecoma, a stromal derivative, is significantly more common in carcinoma of the endometrium than in the control series (9:1).

7. Subinvoluted corpora lutea and theca lutein cysts are seen in the fifth and sixth decades of life, and are more common in cases of endometrial carcinoma than in the control series in the same decades.

8. The existence of hormonal factors in endometrial carcinoma is discussed.

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A CORRELATIVE STUDY OF ADENOMYOSIS AND PELVIC ENDOMETRIOSIS, WITH SPECIAL REFERENCE TO THE HORMONAL REACTION OF ECTOPIC ENDOMETRIUM

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THE term adenomyosis, as it is generally employed, refers to the nonneoplastic condition in which the uterine mucosa exhibits a benign invasion into the uterine musculature. There is no submucosa in the uterus, so that the endometrium is in direct contact with the muscularis, its under surface being closely applied to the latter, and dipping for short distances into the interstices of the musculature. The benign invasion seen in adenomyosis may extend for only a comparatively short distance, or it may penetrate even to the serosa, thus giving rise to a variety of secondary pelvic endometriosis, though not, of course, the common one.

Even in a normal uterus the mucosal indentations into the musculature may at times be fairly deep, so that it is difficult to draw any sharp line between such normal irregularities and actual adenomyosis. In the latter, however, the mucosal invasion is much more pronounced, and is always combined with overgrowth of the muscularis, with grossly a greater or lesser degree of thickening of the uterine wall in the involved areas. The fact that estrogen is the normal growth hormone of both the mucosa and the muscularis has naturally led to the suspicion that adenomyosis is a hormone-induced lesion, but there is certainly no direct evidence on this point.

The abnormal endometrial growth propensity which forms a part of adenomyosis is quite different from that seen with endometrial hyperplasia, the lesion which above all others is believed to be due to an excessive and abnormally persistent estrogen growth effect. While the surface mucosa in cases of adenomyosis may show a typical Swiss cheese hyperplasia, in other cases it may be entirely normal, with a normal response to progesterone as well as to estrogen. The conspicuous growth abnormality of the surface endometrium in the case of adenomyosis is manifested by the downward penetration into the muscularis of a mucosa which normally, whatever its hormonal response may be, respects the normal barrier between the mucosa and the muscularis.

In spite of this distinction, one cannot resist the feeling that there is some common denominator between endometrial hyperplasia and adenomyosis, and possibly also pelvic endometriosis. As a matter of fact, the designation internal or uterine endometriosis is used by many authors for adenomyosis. The wisdom of this seems to us rather doubtful, not only because of the confusion it creates with the common variety of external endometriosis, but even more because the

histogenesis of the internal and external varieties of endometriosis is entirely different, whatever the origin of the external form may actually be. On this latter point there is still much uncertainty, but this question calls for no review in this paper.

The fact that there are certain points in which either the histogenesis or the hormonal responsiveness of these three lesions appear to make contact, and that either two or all three of these not infrequently coexist, made it seem worth while to review our material from this standpoint, and this correlative study constitutes one of the purposes of this paper.

The other has to deal with the fact that in both adenomyosis and pelvic endometriosis we are dealing with ectopic endometrium, and the question arises as to whether this endometrium exhibits hormonal reactions similar to that of the uterine mucosa proper, with which it may be histologically identical. The general statement is often made that it does react to the ovarian hormones just as does the surface mucosa, but our studies indicate that this is not by any means always the case. The investigation of this point constitutes the second purpose of this paper.

Material

The material on which this study is based comprises 243 patients with cases of adenomyosis and pelvic endometriosis which were operated upon in the private service of the senior author in Bon Secours Hospital in the eight-year period extending from 1938 to 1946. Adenomyosis alone was found in 92 cases, pelvic endometriosis alone in 102, while in 42 cases both these lesions were present. In a considerable proportion of all groups, other conditions, such as myomas, were likewise present, but would seem to have no bearing on the present discussion. We may add, also, that the occasional cases of adenomyosis with penetration to the uterine serosa were not included in the series of cases of pelvic endometriosis. In many of the adenomyosis cases one or both ovaries were available for study, and in many of the pelvic endometriosis group the endometrium of the uterus was likewise available, so that correlative studies were all the more readily possible. While, as we shall see, ovarian endometriosis is not uncommon in cases of adenomyosis, our experience convinces us that the frequency of this coexistence would be much greater than we found it if it were possible to study both ovaries thoroughly in all cases. Very frequently, and very properly, one or both ovaries are conserved, but endometriosis is not infrequently present, perhaps deep beneath the surface of such ovaries. This can be stated on the basis of the study of a number of such grossly normal ovaries, or ovaries showing grossly only follicle cysts, which were removed with the uterus in some of our cases of adenomyosis. Not always is ovarian endometriosis a hemorrhagic lesion, and the nonhemorrhagic, usually microscopic lesions, are likely to be overlooked. In any event the fact that in the 243 cases of this series, both adenomyosis and pelvic (usually ovarian) endometriosis were coexistent in no less than 42, is at least suggestive of some sort of relationship between the two.

The general grouping of the 243 cases, together with the age incidence in the various groups, is summarized in Table I.

In the 99 cases showing only adenomyosis, the lesion was of various degrees, the ectopic endometrium being limited to the inner third of the myometrium in 65, involving two-thirds of the muscularis in 23, and the whole thickness in 11 cases.

Adenomyosis With Endometrial Hyperplasia

In 36 of the cases (36.3 per cent) the surface mucosa showed a hyperplasia pattern, while in the remaining 63 (64.9 per cent) it showed one phase or another of a normal estrogen-progesterone cycle, with the exception of two cases in which the endometrium was of senile atrophic type. Since the age of the 36 patients in this group averaged 50.2 years, it is not surprising that the hyperplasia pattern of the endometrium was often of the retrogressed variety seen so often beyond the menopause.

TABLE I

	AGE	21-30	31-40	41-50	51-60	61 AND BEYOND
Adenomyosis without hyperplasia (63 cases)	Number	3	23	31	5	1
Adenomyosis with hyperplasia (36 cases)	Number	–	5	15	12	4
Adenomyosis with endometriosis and without hyperplasia (31 cases)	Number	1	11	15	3	1
Adenomyosis with endometriosis plus hyperplasia (11 cases)	Number	1	2	5	2	1
Endometriosis without hyperplasia (92 cases)	Number	31	39	20	2	–
Endometriosis with hyperplasia (10 cases)	Number	–	3	6	1	–

In no case of this subgroup of 36 cases showing surface hyperplasia was the ectopic endometrium of functioning type. Always it showed a proliferative picture, with a Swiss-cheese hyperplasia in at least 18 cases. In at least one case a large cystic gland was found to be full of blood, indicating that bleeding may occur in islands of purely proliferative ectopic endometrium, just as it may occur from the purely proliferative surface endometrium in cases of anovulatory menstruation.

In the study of our material we were interested to note that the most active and extensive cases of adenomyosis were those in which there was marked hyperplasia of the basal layer of the surface mucosa, whether the latter was of functional or purely proliferative type. It is not uncommon to see a thickened, proliferative basalis, even of Swiss-cheese type, in an otherwise typical progestational endometrium. The basalis represents the growing portion of the mucosa, and is under the hormonal growth influence of estrogen alone, the immaturity of its cells making them unresponsive to the differentiating hormone, progesterone. It is therefore not surprising that when there is a hyperplastic overgrowth of the basalis, the latter may give further evidence of its proliferative tendency by pushing down into the muscularis, with the production of adenomyosis.

The ovaries were available for study in 20 of the 36 cases in this hyperplasia group. All of them showed follicle cysts with or without well preserved granulosa cells, which might be expected. However, in three cases corpus luteum structures were noted, including two of corpus luteum hematoma and one of corpus luteum cyst. An occasional corpus luteum in cases of hyperplasia has been noted by others (Novak and Martzloff). The finding of corpus luteum structures, active or retrogressive, in such cases is probably to be interpreted as representing beginning ovulatory activity in previously anovulatory women or relics of previous ovulations in women who more recently have been anovulatory.

Adenomyosis Without Hyperplasia of the Endometrium

In this group there were 63 cases, varying in age from 24 to 64 years, and they may be subdivided into the following groups.

(a) Progestational endometrium was noted in 14 cases, and the most striking feature of this group was that, without a single exception, the invading islands of endometrium in the uterine wall were of nonsecretory type, and in none of these was there any evidence of blood. All the ectopic endometrium, therefore, was of the unripe, immature variety responsive only to estrogen, but not to progesterone. In six of the cases the ectopic endometrium showed a Swiss-cheese hyperplasia, in seven it was of early interval type, and in one it resembled the postmenstrual phase. It is of further interest that in four of the six cases in which the ectopic mucosa showed hyperplasia, there was similar marked hyper-

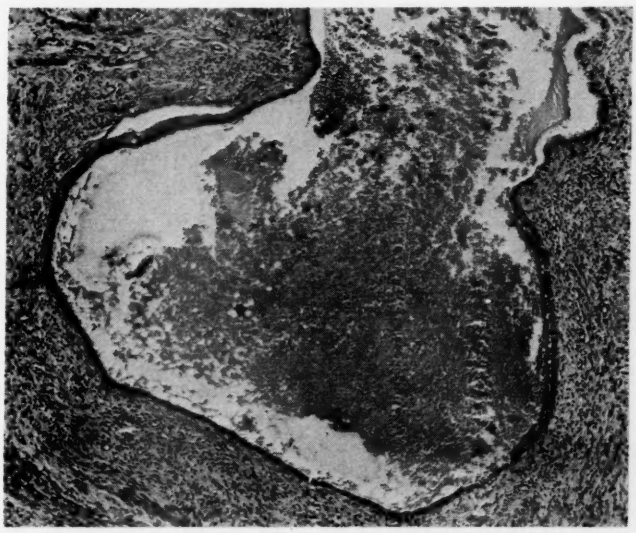

Fig. 1.—High power of blood-containing gland in ectopic endometrium of a case of adenomyosis, the surface mucosa showing hyperplasia.

plasia of the basalis of the otherwise progestational surface mucosa. The significance of this fact, as indicating the probable origin of adenomyosis from the basalis, has already been commented upon.

(b) Proliferative, nonsecretory surface endometrium was noted in 17 cases, 13 corresponding to an early interval phase, and 4 postmenstrual. In every one of these the ectopic mucosa was likewise of proliferative type. In only 1 case was there evidence of bleeding in the invading endometrial islands, a large dilated gland showing a considerable amount of blood within its lumen. The ovaries of this case were not available for study, but it seems reasonable, in view of the proliferative picture of both the surface and the invading mucosa, that the cycles were probably of anovulatory type. There is no reason why bleeding might not occur in the ectopic mucosa of anovulatory patients, just as it occurs from the surface mucosa, usually with only slight evidence of histologic regression.

(c) Menstruating endometrium was found on the surface of seven uteri which were removed during a menstrual period, in six of ovulatory, and one of anovulatory variety, on the basis of correlated ovarian study. The aberrant

endometrium in every case was of nonsecretory type, five showing Swiss-cheese hyperplasia, and two an early interval picture. This again emphasizes the immature nature of the invading endometrium.

(d) Decidual changes in the surface mucosa were seen in two cases in which there had been a recent pregnancy, although no villi were seen. In one case, however, one of the ovaries was available for study, and it showed a typical corpus luteum of pregnancy. No evidence of decidual change was seen in the ectopic endometrium of either of these cases, again illustrating the usual refractoriness of the ectopic endometrium to the full hormonal response of which the functional layers of normal endometrium are normally capable. There are, of course, exceptions to this rule, since the aberrant mucosa is certainly in a minority of cases of functioning type, which can under the influence of both estrogen and progesterone exhibit either progestational or even decidual changes, as we have observed in an occasional case.

(d) Senile surface endometrium was seen in two cases, with similar changes in the aberrant mucosa.

Adenomyosis Combined With Pelvic Endometriosis

In 42 patients there was a co-existence of adenomyosis and pelvic endometriosis. The adenomyosis in 31 of the cases was limited to the inner third of the muscularis, the inner two-thirds in six, and it involved the whole thickness of the uterine wall in three. The pelvic endometriosis, with some overlapping of groups, involved the ovaries in thirty-two cases (five bilateral), the tubes in nine (three bilateral), the pelvic serosa in two, and the appendix in one (no other pelvic endometriosis).

In eleven cases the surface mucosa of the uterus showed a typical Swiss-cheese hyperplasia, while in the remaining thirty-one it was presumably of fully cyclical type (seventeen secretory, nine interval nonsecretory, three postmenstrual, one menstrual, and one senile).

(a) In the eleven patients with surface hyperplasia, the ectopic mucosa was in every case of proliferative variety, showing Swiss-cheese hyperplasia in six, interval nonsecretory in three, and postmenstrual in two. No blood was found in the gland lumina of any of these cases.

In the eleven cases of this group the associated endometriosis involved the ovaries alone in nine, the tubes alone in one, and both ovaries and tubes in one. In contrast with the invading endometrium of adenomyosis the ectopic pelvic endometriosis characteristically shows a hemorrhagic tendency, this appearing in nine cases. In six of these, typical endometrial blood-containing ovarian cysts were noted. In none of them, however, was there any evidence of secretory response, just as was found with the aberrant endometrium of adenomyosis, suggesting that in both conditions the ectopic endometrium is of immature, not fully functioning type.

(b) In 31 cases of combined adenomyosis and pelvic endometriosis in which the uterine surface mucosa was presumably of functional type, the ectopic endometrium of the adenomyosis was of nonsecretory type in every case. The aberrant mucosa of the pelvic endometrium was not so easily analyzed, as in a considerable group endometrial cysts were present in which much of the mucosa was lost. In one such case secretory glands were seen adjoining such a cyst, and it is quite possible that in others the mucosa might also have been of functioning type, though this could not be demonstrated histologically. The presence of the blood cannot be considered as definite evidence of an estrogen-progesterone type of menstrual bleeding, as bleeding can also occur from endometria as a result of estrogen stimulation alone. The fact that hemorrhage is so much more common in the aberrant endometrium of pelvic endometriosis than that of adeno-

myosis might suggest that a full menstrual response is more common with the former, but histologic proof of this is difficult. Again, no conclusions can be drawn from the twelve cases in which the ectopic pelvic endometrium was of interval nonsecretory or postmenstrual type, as endometrium of these types might occur whether the cycles are ovulatory or nonovulatory. In the one case

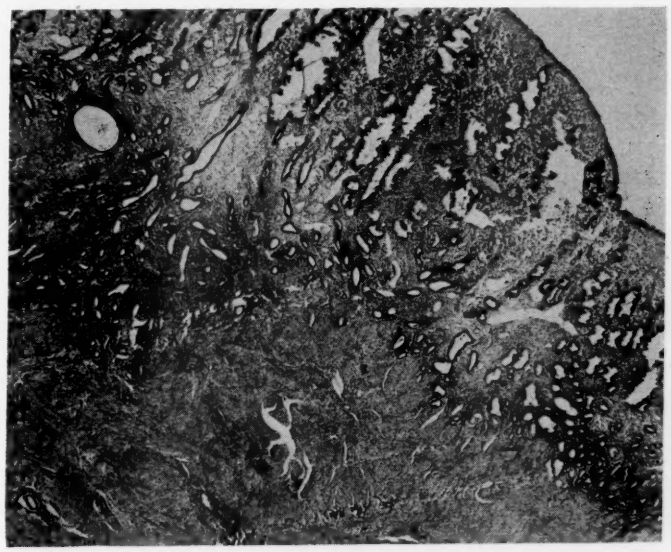

Fig. 2.—Showing invading basalis in case of adenomyosis, the surface mucosa being typically progestational. Pelvic endometriosis was also present in this case, the aberrant endometrium being of immature, nonsecretory type.

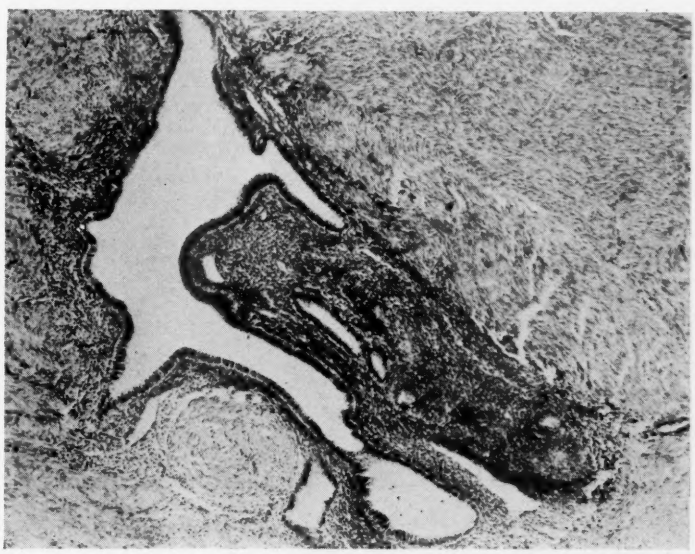

Fig. 3.—An area of immature, nonsecretory type deep in the muscularis of case shown in Fig. 2.

of this group in which operation was done on the first day of menstruation, the presence of a few desquamating secretory cells on the surface of the endometrial cyst make it seem certain that the endometrium was of fully functioning type.

Pelvic Endometriosis Alone

In this series there were 102 cases of pelvic endometriosis, without associated adenomyosis. In 53 of these the uterus was available for study, having been removed either because of extensive endometriosis in women of the older age

Fig. 4.—Showing how the basalis invades the muscularis in a case of adenomyosis.

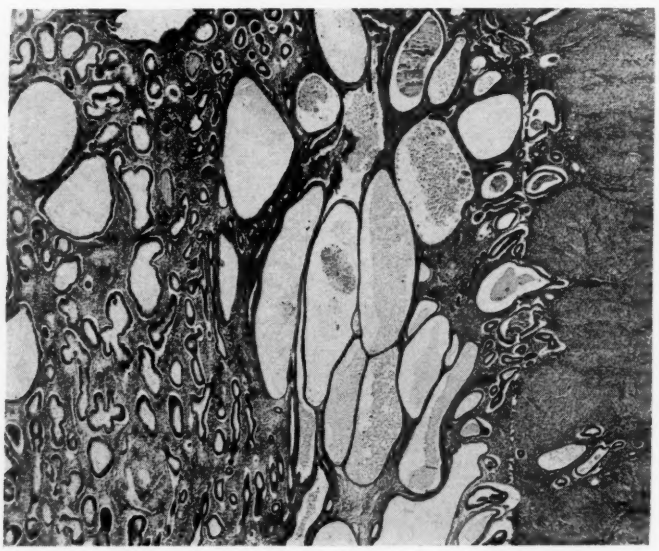

Fig. 5.—Marked Swiss-cheese hyperplasia pattern of basalis in a case of adenomyosis.

group, or for other indications, usually uterine myoma. In eleven others curettage had been done, so that the endometrium was available for study. The following sites of endometriosis were noted: ovaries, eighty-four; tubes, fifteen; uterine serosa, five; appendix, six; sigmoid, one; rectum, three; vesicouterine peritoneum, two; and broad ligament, one.

A correlative histologic study of the surface mucosa of the uterus and the ectopic pelvic peritoneum was therefore possible in 64 cases, while in the remaining 38 the only correlation possible was between the chronological menstrual phase and the histology.

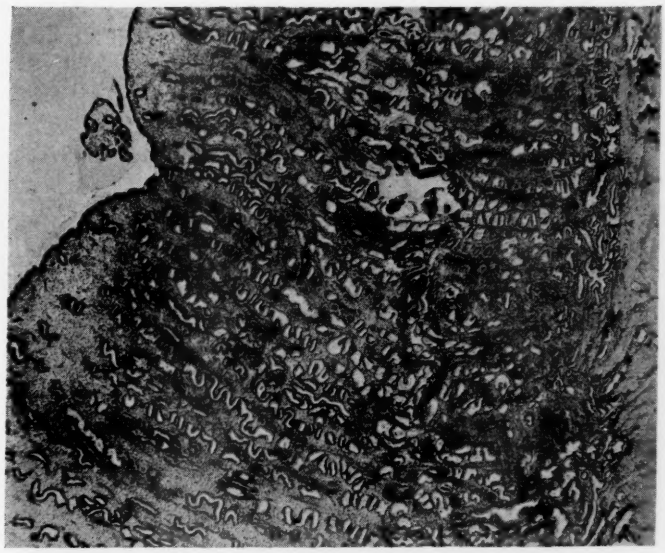

Fig. 6.—Typical progestational endometrium of uterus in which the aberrant ovarian endometrium is of proliferative, nonsecretory variety (see Fig. 7).

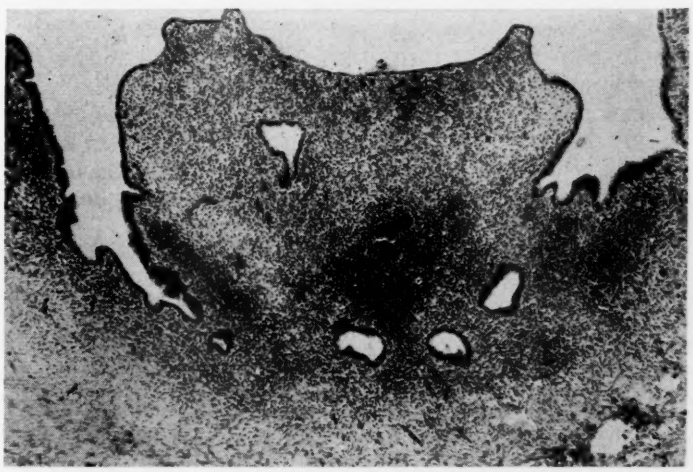

Fig. 7.—Immature nonsecretory endometrium in ovary of case showing marked progestational endometrium in uterus. (Fig. 6.)

In ten cases in which the uterine mucosa showed a Swiss-cheese hyperplasia the aberrant pelvic endometrium showed also a proliferative endometrium. In the remaining 54, the uterine endometrium was of secretory, early interval or postmenstrual variety and presumably of fully functioning type. Only six showed definite secretory changes in the pelvic endometrium, but it is quite sure that a number of others, especially those with definite chocolate cysts, were likewise of this type, though we could not demonstrate this histologically.

The common finding of blood in pelvic endometrial lesions cannot be linked up with a recent menstrual period, as the blood persists and is to be found at any phase of the cycle. In three of the cases in this group the operation had been done during a menstrual bleeding, and in two of these, on the basis of the absence of any corpus luteum in the ovaries, the cycles were thought to be anovulatory. In both of these the ovarian endometrium was of Swiss-cheese type.

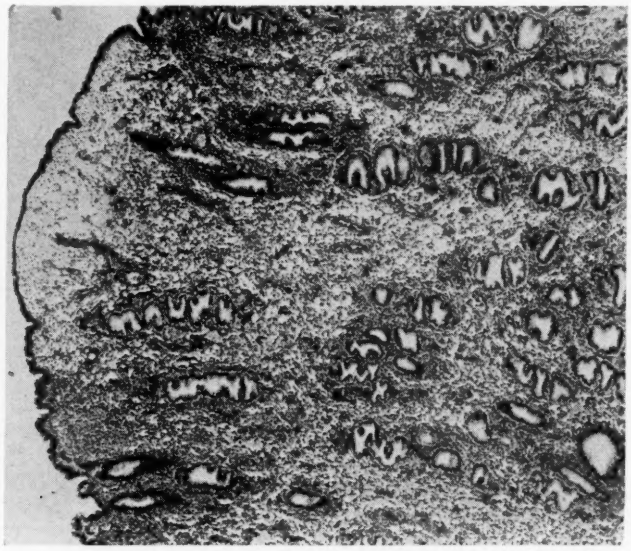

Fig. 8.—Progestational endometrium in uterus with nonsecretory endometrium in ovary (see Fig. 9).

Finally, there remains the group of 38 cases of endometriosis in which neither the uterus nor even the curetted mucosa were available for study, and in which no correlation was possible except on the basis of menstrual chronology. Because of the very limited value of this group in our present study we shall not detail the findings. Suffice it to say that almost without exception the pelvic endometrial islands were of proliferative, nonfunctioning type.

Incidence of Endometrial Hyperplasia With Adenomyosis and Pelvic Endometriosis

The frequent co-existence of endometrial hyperplasia with both adenomyosis and endometriosis has been noted by various authors (Novak and Martzloff, Jeffcoate and Potter, Witherspoon, Smith, Haydon, and others). In our series the incidence of this combination was 23.4 per cent for the entire group, comprising 36.3 per cent in the cases of adenomyosis alone, 9.8 per cent in those of pelvic endometriosis, and 26.1 per cent in those with both adenomyosis and endometriosis.

The fact that adenomyosis and pelvic endometriosis so frequently coexist is at least suggestive of some common denominator in their causation, most likely hormonal. However, since we know so little of the etiology of either condition, especially adenomyosis, we can for the present only speculate as to the nature of their relation. Hyperplasia of the endometrium may perhaps be drawn into this group of possibly interrelated lesions, since it is frequently found combined with the other two. The fact that there are numerous exceptions to this last named combination does not negate the possibility of some sort of common denominator between them.

Coexistence of Myoma With Adenomyosis and Pelvic Endometriosis

The incidence of myoma in our series of 243 cases of adenomyosis and endometriosis was 37.5 per cent for the former and 29.8 per cent for the latter, or 33.7 per cent for the combined group. This is somewhat lower than the figures for similar groups reported by others (Fallas and Rosenblum, 41.5 per cent; Smith, 41.6 per cent). The association of myoma with these lesions is probably coincidental, as myoma is a definite neoplasm of unknown etiology, and there is little support for the hypothesis that it may be of endocrine causation. On the other hand, neither adenomyosis nor endometriosis are neoplastic, and there is more justification for suspecting the possibility of an endocrine factor in their production.

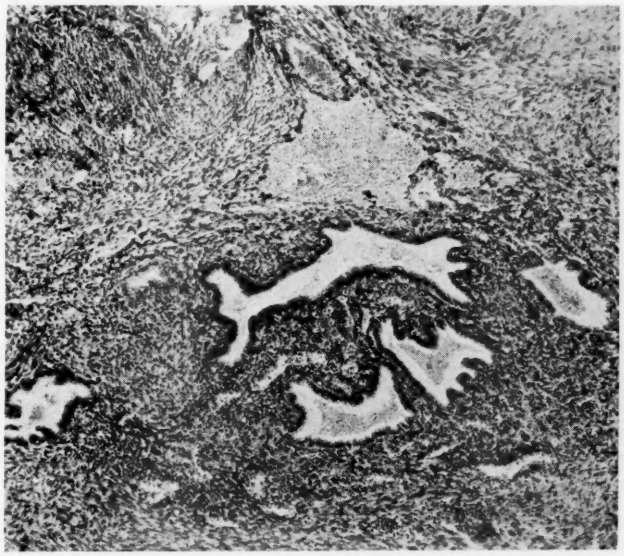

Fig. 9.—Nonsecretory endometrium in ovary, associated with progestational endometrium in uterus (Fig. 8).

Comment and Summary

The existence of a definite hyperplasia of the endometrium is commonly taken to be evidence of an anovulatory cycle, but this interpretation is acceptable only when applied to the uterine surface mucosa. It would not be justified from examination of the ectopic endometrium of adenomyosis and endometriosis, since this is often of hyperplastic type even when the surface mucosa is secretory. We therefore disagree with the suggestion of von Numers that anovulatory cycles, assumed only on the basis of examination of the ectopic endometrium, may actually be of importance in the production of adenomyosis and pelvic endometriosis, or that they necessarily explain the common sterility seen with the latter. It is obvious, also, from the results of our own studies, that we cannot agree with the statement of Jeffcoate and Potter that "since the ectopic endometrium reacts to ovarian hormones in exactly the same way as does the uterine mucosa, its histologic appearance permits an estimation of ovarian function normal or otherwise."

The incorrectness of this statement, aside from the objective evidence we have presented, is explained by the fact that the aberrant endometrium of both adenomyosis and endometriosis is usually of an immature variety, its immaturity being evidenced by the fact that it is physiologically responsive only to the growth stimulus of estrogen, and not to the differentiating influence of progesterone. There are, of course, some exceptions, the exact incidence of which it is difficult to set down with any accuracy, because of the frequent difficulty, especially in ovarian endometriosis, of gauging the functional status of the lining of hemorrhagic cysts from which most of the lining has been lost.

It so happened that in the present series the ectopic endometrium of adenomyosis showed no histologic evidence of secretory activity in any case, regardless of whether or not the surface mucosa was of secretory type. This was rather surprising to us, since we have noted secretory changes in the ectopic mucosa of at least an occasional case of adenomyosis, though none was encountered in this particular series. Certainly, however, there can be no doubt that in the vast majority of cases the ectopic endometrium is of immature type, responding to the growth effect of estrogen but not to the differentiating effect of progesterone.

Another interesting feature of the general problem has been the common occurrence of bleeding in ovarian and other forms of pelvic endometriosis, and to a far smaller extent in the aberrant mucosa of adenomyosis, even when such ectopic endometrium is clearly of purely proliferative type. This, after all, is not surprising, since anovulatory menstruation and anovulatory functional bleeding have their source from a purely proliferative uterine surface mucosa. Just why this hemorrhagic tendency is so much more marked in the case of endometriosis than in that of adenomyosis is not clear, although one factor which suggests itself is the immediate proximity of the ovarian endometrium to the source of production of the ovarian hormones.

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PREGNANCY AND SUBACUTE BACTERIAL ENDOCARDITIS*

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PRIOR to the introduction of antibiotics, particularly penicillin and, to a more limited extent, streptomycin, subacute bacterial endocarditis was usually a fatal disease. Pregnancy was rarely complicated by this condition and therapy in the presulfonamide and sulfonamide eras was directed toward supporting the strength of the mother in the hope of obtaining a living child.

Stander[1] was able to find only eighteen authenticated cases of subacute bacterial endocarditis in pregnancy. The development of effective antibiotics has greatly improved the outlook for the patient with this disease and has created a relatively new problem in obstetrics. Hamilton[2] sent questionnaires to obstetricians and cardiologists and reports were received of seventeen women treated with penicillin for subacute bacterial endocarditis during pregnancy or the puerperium. Six died during pregnancy and three others died within the next five months, giving a total mortality of 53 per cent. The fetal mortality was 24 per cent. Eleven patients cured of the disease prior to pregnancy all survived childbirth. Three of the eleven were aborted therapeutically. Dobson[3] reported a case of subacute bacterial endocarditis during pregnancy in which hysterotomy was performed at eighteen weeks' gestation "because it was felt that pregnancy might have an unfavorable influence on the course of the disease." The patient recovered. Davis and Wortmann[4] also reported a case during pregnancy, cured with penicillin and carried to viability, at which time a cesarean section and hysterectomy were performed. There had been two previous cesarean sections for cephalopelvic disproportion. The patient obtained a living child but had serious residual cardiac damage.

Present Study

There have been ten cases with a diagnosis of subacute bacterial endocarditis complicating pregnancy in some 50,000 patients at the New York Lying-In Hospital from 1932 through 1947. The incidence of this complication is 0.02 per cent. Three cases with positive blood cultures occurred before the use of penicillin and all died during pregnancy or the puerperium. Seven cases, treated with penicillin, survived pregnancy and delivered normal living children. Two of the penicillin-treated cases had clinically authentic subacute bacterial endocarditis during pregnancy, unconfirmed by positive blood cultures. Five of the penicillin-treated cases were proved by positive blood cultures: three had recently recovered from the disease prior to the pregnancy under consideration, and two developed the disease during pregnancy. The purpose of this study is to review these five proved cases treated with penicillin in an attempt to evaluate the significance of subacute bacterial endocarditis prior to and during pregnancy. Table I summarizes the experience with the five patients.

*Read before the Section of Obstetrics and Gynecology of the New York Academy of Medicine on Feb. 24, 1948.

TABLE I. ANALYSIS OF DATA
CASES OF PROVED SUBACUTE BACTERIAL ENDOCARDITIS TREATED WITH PENICILLIN

CASE	PATIENT	AGE	PARITY	GRAVIDITY	PELVIS	CARDIAC DIAGNOSIS	COMMENT
1.	G. O.	34	2	3	Normal	Rheumatic Enlarged heart MI MS N. S. R. Class 1B	S. B. E. 8 months prior to pregnancy Vaginal delivery. Mother, baby well
2.	I. J.	38	4	6	Normal	Rheumatic Enlarged heart MI MS N. S. R. Class 2B	S. B. E. 12 months prior to pregnancy Vaginal delivery. Mother, baby well
3.	C. L.	17	0	1	Normal	Rheumatic Enlarged heart MI MS AI N. S. R. Class 1B	S. B. E. 17 months prior to pregnancy Vaginal delivery. Mother, baby well
4.	F. J.	27	0	2	Normal	Rheumatic Enlarged heart MI MS N. S. R. Class 3C-4E	S. B. E. in fifth month of pregnancy Vaginal delivery. Mother, baby well
5.	V. D.	25	1	2	Normal	Rheumatic Enlarged heart MI MS N. S. R. Class 3C-4E	S. B. E. in eighth month of pregnancy Vaginal delivery. Mother, baby well

MI-Mitral insufficiency
MS-Mitral stenosis
AI-Aortic insufficiency
N. S. R. Normal sinus rhythm
Class-Functional and therapeutic of the New York Heart Association (see text)
S. B. E. Subacute bacterial endocarditis

CASE 1.—G. O. Subacute bacterial endocarditis in April, 1945. Blood cultures showed *streptococcus viridans* sensitive to 0.08 units of penicillin per c.c. The patient received 32 million units of penicillin over forty-two days and recovered. All subsequent blood cultures were negative. She became pregnant eight months later, at which time the heart showed slight enlargement but the electrocardiogram, vital capacity (4,000 c.c.), and exercise tolerance were normal. The functional classification was 1B. Pregnancy was allowed to continue. The patient went through an entirely uneventful pregnancy and labor without any evidence of cardiac strain. She had a fifteen-hour labor at 42 weeks' gestation and was delivered by low forceps under gas, oxygen, ether anesthesia. The baby weighed 3,600 Gm. The pulse and respirations remained normal throughout labor. The blood loss at delivery was estimated at 150 c.c. Penicillin was given for three days postpartum and mother and baby were discharged well on the tenth day. Follow-up examination one year later revealed no change in the cardiac status.

CASE 2.—I. H. Subacute bacterial endocarditis in May, 1945. Blood cultures showed *streptococcus viridans* sensitive to 0.08 units of penicillin per c.c. The patient received seven million units of penicillin over twenty-six days and recovered in spite of an embolus to the right femoral artery. All subsequent blood cultures were negative. In July, 1945, a cholecystostomy and choledochotomy were performed. The patient received penicillin for the first two days after operation and recovery was uneventful. She became pregnant in May, 1946, and was admitted to the hospital for study in the third month of pregnancy. The heart showed slight enlargement but the electrocardiogram, vital capacity (3,100 c.c.), circulation time, and exercise tolerance were normal. The functional classification was 2B. The blood

pressure was 140/90 but the eyeground and renal function tests, including blood chemistry, urea clearance, dye excretion, and dilution concentration were all normal. The pregnancy was allowed to continue and the patient was discharged, to be followed in the antepartum cardiac clinic. The course was uneventful until the fifth month, when the patient developed an attack of bronchitis. She was admitted to the hospital, digitalized, and given penicillin for three days. Blood cultures were negative and recovery was complete without evidence of cardiac embarrassment. She was discharged on the ninth day after admission and was again followed in the cardiac clinic until the eighth month when readmission was advised because of mild pre-eclampsia. The cardiac status had remained unchanged. The patient remained in the hospital on a toxemia regimen and improved. She had a normal spontaneous delivery under open-drop ether, after eight hours of labor at term. The baby weighed 3,420 Gm. The pulse and respirations remained normal throughout labor. The blood loss at delivery was measured at 100 c.c. Penicillin was given for five days. Because of the age and parity and development of eyeground changes, tubal ligation was performed under gas-oxygen-ether anesthesia on the fourth postpartum day. Recovery was uneventful and mother and baby were discharged well on the thirteenth postoperative day. Follow-up examination six months later revealed no change in the cardiac status.

CASE 3.—C. L. Subacute bacterial endocarditis in May, 1945. Blood cultures showed *streptococcus viridans* sensitive to 0.04 units of penicillin per c.c. The patient received ten million units of penicillin over thirty-three days and recovered. All subsequent blood cultures were negative. She became pregnant seventeen months later and was admitted for study in the third month of gestation. X-rays, electrocardiogram, circulation time, vital capacity (3,600 c.c.), and exercise tolerance were normal. The functional classification was 1B. Pregnancy was allowed to continue and the patient was discharged to be followed in the antepartum cardiac clinic. Because of obesity, she was placed on a 1,200 calorie diet. Pregnancy was entirely uneventful and admission was advised for observation several weeks prior to the expected date of confinement. Digitalis was not given. The patient had a normal spontaneous delivery under open-drop ether after an eighteen hour labor at 42 weeks' gestation. The baby weighed 3,610 Gm. The pulse and respirations remained normal throughout labor. The blood loss at delivery was measured at 350 c.c. Penicillin was given for three days postpartum and the puerperium was normal. Mother and baby were discharged well on the tenth postpartum day. Follow-up examination six weeks later revealed no change in the cardiac status.

CASE 4.—F. J. The patient was seen in the fourth month of pregnancy at which time studies revealed cardiac enlargement, electrocardiographic evidence of myocardial damage, impaired vital capacity (2,300 c.c.), and decreased exercise tolerance. The functional classification was 3C. Pregnancy was allowed to continue, since gestation was too far advanced for vaginal interruption and hysterotomy seemed ill advised. The patient left the hospital against advice and re-appeared in the fifth month with a history of upper respiratory infection, chills, fever, and weakness. Examination revealed evidence of cardiac failure, petechiae, splenomegaly, and marked anemia. Blood cultures revealed *streptococcus viridans* and a diagnosis of subacute bacterial endocarditis was established. The organism was sensitive to 0.175 units of penicillin per c.c. The patient received a total of ten million units of penicillin over twenty-eight days and recovered, all subsequent blood cultures being negative. Digitalis was given; sodium, fluid, and activity were limited, and the cardiac status improved markedly. Two small transfusions were given. The patient remained in the hospital and was delivered by midforceps under local anesthesia, after a prolonged labor of fifty-eight hours at term. The baby weighed 3,590 Gm. During labor, the pulse reached 126 and the respirations 32. The upright position in an oxygen tent was maintained throughout labor and delivery and immediately postpartum. The blood loss at delivery was measured at 200 c.c. Penicillin was administered during labor and the first week post partum. The cardiac status improved after delivery and the patient and baby were discharged well three weeks later. Therapeutic abortion of a two months' pregnancy was performed one year later at which time the cardiac classification was 3C.

CASE 5.—V. D. The patient was first seen in the eighth month of pregnancy, with the classical picture of subacute bacterial endocarditis and early cardiac decompensation. Blood cultures revealed *streptococcus viridans* sensitive to 0.13 units of penicillin per c.c. Penicillin was started together with digitalis and other cardiac measures. Several days after admission, the patient developed a mesenteric infarct and went into spontaneous premature labor. After two hours of labor, she had a normal delivery under open-drop ether. The baby weighed 1,860 Gm., was transferred to the premature nursery, and survived. The mother's pulse remained above 120 and the respirations above 36 throughout labor. The blood loss at delivery was measured at 100 c.c. The patient also received sulfadiazine with soda bicarbonate for the first two days postpartum. Decompensation became more marked and the patient had to be placed in an oxygen tent. The postpartum course was febrile and further complicated by multiple emboli to the spleen, extremities, and brain. Heparin was started on the third postpartum day, followed by dicumarol. The latter was stopped six days later when evidence of subarachnoid hemorrhage developed. A total of 18 million units of penicillin was given. The patient recovered after a stormy and critical course.

Discussion

Subacute Bacterial Endocarditis Prior to Pregnancy.—The cases in the literature as well as those reported in this study, indicate that a past history of subacute bacterial endocarditis is not necessarily a contraindication to subsequent pregnancy. Healing of the endocardial lesions may result in progressive scarring and calcification of the heart valve. Moore[5] concludes from autopsy studies that it takes from three to six months for complete healing. The intervals between subacute bacterial endocarditis and pregnancy were eight, twelve, and seventeen months in the present series. The cardiac pathology had become stabilized in all three patients. It would appear advisable to defer pregnancy until at least six months after the disease has been cured. This interval would allow for the possibility of relapse. The advisability of childbearing should then be determined by the current cardiac status, and accepted concepts of management of the underlying heart disease followed during pregnancy, delivery, and the puerperium. Most cases of subacute bacterial endocarditis occur where the valvular endocardium has been congenitally deformed or damaged by rheumatic fever. Many of the features of the management of rheumatic heart disease complicating pregnancy have been illustrated in the foregoing cases. A comprehensive outline follows:

The cardiac status is evaluated when the patient is first seen. Information is obtained regarding age, history, general physical condition, anatomic lesion, heart size as determined by anteroposterior and lateral roentgen studies, electrocardiographic findings, vital capacity, and exercise tolerance. The exercise test should not be performed indiscriminately in the patient with borderline cardiac reserve, for the test itself may cause decompensation. The patient is then classified according to the criteria of the New York Heart Association:

CLASS 1.—Patients with cardiac disease and no limitation of physical activity. Ordinary activity does not cause discomfort. Patients in this class do not have symptoms of cardiac insufficiency nor do they experience anginal pain.

CLASS 2.—Patients with cardiac disease and slight limitation of physical activity. They are comfortable at rest. If ordinary physical activity is undertaken, discomfort results in the form of undue fatigue, palpitation, dyspnea or anginal pain.

CLASS 3.—Patients with cardiac disease and marked limitation of physical activity. They are comfortable at rest. Discomfort in the form of undue fatigue, palpitation, dyspnea, or anginal pain, is caused by less than ordinary activity.

CLASS 4.—Patients with cardiac disease who are unable to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency, or of anginal syndrome, are present, even at rest. If any physical activity is undertaken, discomfort is increased.

As the functional capacity does not always determine the amount of physical activity which should be permitted, the following "Therapeutic Classification" is added as a guide to management:

CLASS A.—Patients with cardiac disease whose physical activity need not be restricted.

CLASS B.—Patients with cardiac disease whose ordinary physical activity need not be restricted, but who should be advised against unusually severe or competitive efforts.

CLASS C.—Patients with cardiac disease whose ordinary physical activity should be moderately restricted, and whose more strenuous habitual efforts should be discontinued.

CLASS D.—Patients with cardiac disease whose ordinary physical activity should be markedly restricted.

CLASS E.—Patients with cardiac disease who should be at complete rest, confined to bed or chair.

Hamilton and Thomson[6] prefer to classify patients as "favorable" or "unfavorable," the latter including those with history or signs of congestive failure, dangerous disorder of the heartbeat, or serious complicating disease. Twenty per cent of the "favorable" cases revert to "unfavorable" during the course of pregnancy.

We have gained considerable prognostic confidence in the classification of the New York Heart Association. Experience has shown that the vast majority of Class 1 and Class 2 patients go through pregnancy and labor without serious cardiac difficulty, and they are followed in the special antepartum cardiac clinic by an obstetrician and cardiologist.

Class 3 and Class 4 patients constitute about 15 per cent of all cardiacs and they present the real problems in management. Admission is advised at the first visit, and cardiac measures are prescribed as indicated until compensation has been satisfactorily restored. The cardiac burden was formerly thought to increase progressively throughout gestation and it was common practice to interrupt pregnancy in the second or third trimester. We have since learned that the cardiac burden begins to rise significantly about the fifth month and reaches a peak in the last trimester, with definite amelioration in the last month. If pregnancy is less than five months advanced, and provided the patient agrees, interruption may be performed by vaginal therapeutic abortion, or abdominal hysterotomy, depending upon the size of the uterus. It may also be justifiable to interrupt early pregnancy in patients, who, despite adequate current cardiac reserve (Class 1 or Class 2), may have recovered from subacute bacterial endocarditis during the preceding six months. The cardiac reserve may possibly change, due to delayed valvular damage incident to the healing process. Tubal

sterilization is frequently performed at the time of hysterotomy. Associated pelvic pathology may occasionally favor interruption and sterilization by hysterectomy. Interference is withheld if the patient has reached the fifth month and she is carried to term anticipating the spontaneous improvement in the last month of pregnancy. The very exceptional patient, with a tight mitral valve, may become progressively worse and die undelivered. It has been suggested that late hysterotomy might avert this fatal outcome, but the impression is gained that, under ideal conditions of care, this situation will rarely be encountered. There is great risk in discharging the patient from the hospital once cardiac failure has occurred antepartum, even though she may have completely recovered from the episode of failure. The mortality in Class 4 is about 15 per cent.

Sodium, fluid, and activity are restricted. Cardiologists have recently stressed that it is unnecessary to limit fluids if sodium is curtailed. It is practically impossible, however, to give an adequate pregnancy diet without at least two to three grams of sodium, and, for this reason, we have insisted on the limitation of fluids. Anemia and obesity should be corrected to remove extra cardiac work. If digitalis has not already been required, it is frequently started in the last trimester, in anticipation of the peak of the cardiac burden. In some instances, the Class 3 patient may have been discharged and closely followed on the same regimen in the cardiac clinic. Sexual relations are interdicted. Readmission is usually advised at the height of the circulatory burden. Oppel[7] has shown that serious upper respiratory infections may precipitate decompensation. Therefore, hospital treatment is recommended in the event of a bad cold or bronchitis, and penicillin is given to prevent subacute bacterial endocarditis. Antibiotics are also given in the event of other serious infection, or dental extraction.

The unsatisfactory obstetric and cardiac results which followed induction of premature labor led to the use of cesarean section for premature delivery. Knowledge of the late physiologic amelioration of the cardiac burden led to the abandonment of any type of premature interference but until recent years the trend to abdominal delivery persisted. Whereas patients with rheumatic heart disease did not tolerate the usual desultory labor produced by premature induction, it has since been shown[8] that they do tolerate the more satisfactory type of labor which occurs spontaneously at term. In fact, vaginal delivery has been shown to be safer than abdominal delivery. This does not imply that cesarean section should not be performed in a cardiac with an obstetric indication such as placenta previa, cephalopelvic disproportion, dystocia labor, etc., but it does mean that cesarean section is seldom if ever indicated because of the rheumatic heart disease per se. The vast majority of patients can be successfully delivered by the vaginal route and the hazards of labor reduced with continuity of treatment including careful functional evaluation, good antepartum care, adequate digitalization, and shortening of the second stage of labor. Brown and her associates[9] have suggested that vaginal delivery is better tolerated than cesarean section because the repeated uterine contractions of labor prepare the

cardiovascular system for permanent occlusion of the placental circulation by gradual diminution of total blood volume. The uterine contractions diminish arterial inflow to the placenta and increase the outflow causing small autotransfusions. These theoretically produce transient rises in the venous pressure and capillary filtration decreases the total blood volume.

The pulse and respiratory rates intrapartum provide a valuable guide to the cardiac status, for it has been observed[10, 11] that elevation of the pulse rate above 110 per minute with a respiratory rate above 24 per minute, or such elevation of the pulse rate alone during the first stage of labor, preceded each instance of intrapartum or postpartum heart failure by a long enough period to provide ample warning of its approach. Conversely, 50 per cent of patients displaying this reaction went on to decompensation. Accordingly, any patient showing these pulse and respiratory rates during the first stage of labor should be rapidly and completely digitalized if this has not already been accomplished. She should be kept upright in bed, given oxygen, and delivered as soon as feasible after full cervical dilatation to avoid the bearing down efforts of the second stage of labor. The upright position and oxygen should be maintained throughout delivery and at least the first twenty-four hours post partum. In the event of frank decompensation, atropine, aminophylline, and bloodless tourniquet phlebotomy are employed. Analgesia is used during labor as indicated but restlessness and excitement are avoided. Local anesthesia or open-drop ether is safest for delivery. The drop in blood pressure which may accompany caudal block or spinal anesthesia makes these agents undesirable. Whereas cyclopropane allows for the administration of relatively large oxygen concentration, this anesthetic is contraindicated because of its tendency to produce cardiac arrhythmias. The incidence of spontaneous abortion and premature labor, the infantile mortality, the duration of labor, and the blood loss at delivery, in women with serious rheumatic heart disease, are not significantly different from values in normal women.[8] Early puerperal ambulation is encouraged as soon as the cardiac status warrants. Breast feeding is not advocated because of increased physiologic demands and dangers of mastitis.

Wheeler[12] found evidence of a precipitating factor in 54 of 200 cases of subacute bacterial endocarditis. Nine of these were ascribable to abortion or delivery, such causes being second in incidence only to upper respiratory infection. Accordingly, we have advocated the prophylactic use of antibiotics during labor and the puerperium. If sulfonamides are also administered, care should be exercised in the concomitant use of large amounts of soda bicarbonate to prevent crystal formation. If bicarbonate is given in the recommended ratio of 4 Gm. to 1 Gm. of sulfonamide, fluid retention may develop to a dangerous degree.

The cardiac regimen as outlined above requires all the skill and niceties of medical and surgical obstetrics, and only when these are available should one feel justified in assuming the responsibility for pregnancy complicated by serious rheumatic heart disease.

We have had no experience with subacute bacterial endocarditis in congenital heart disease during pregnancy, but the obstetric management of patients

with congenital heart disease[13] is essentially the same as that for rheumatic cardiac patients. The majority with serious congenital heart disease succumb before reaching puberty. Cyanosis per se is not a contraindication to pregnancy. The dangers of a venoarterial shunt must be kept in mind. Coarctation of the aorta was found to present a special problem for, in this unusual condition, the functional classification is not necessarily related to the immediate prognosis because of the ever-present danger of rupture of the pathologically thinned aorta or cerebral vessels. A study of 29 cases of this condition showed that about half the patients suffered a deleterious effect from childbearing. Five died during pregnancy or shortly after delivery (two from rupture of the aorta, one from cerebral accident, one from cardiac failure, and one from endocarditis). Ten patients, surviving pregnancy, were definitely made worse by it. It was felt that pregnancy and labor presented such risks to patients with coarctation of the aorta that therapeutic abortion may be indicated or delivery by cesarean section advised.

Subacute Bacterial Endocarditis During Pregnancy.—There is insufficient evidence to date, to suggest that the development of subacute bacterial endocarditis during pregnancy significantly alters the management of pregnancy, delivery, or the puerperium, as outlined above. Fever accompanying the illness might induce abortion or premature labor. Case 4 carried to term despite a transient febrile course. Whereas Case 5 delivered prematurely, she had delivered at the same period of gestation in her previous pregnancy.

The fear that pregnancy may exert an unfavorable influence on the course of subacute bacterial endocarditis has already been mentioned. The incidence of heart failure complicating the disease might be increased due to the added burden of pregnancy. Regardless of the extra load imposed, it would appear inadvisable to interfere during the acute phase of the disease. Once the disease is under control, anticipation of subsequent valvular damage incompatible with pregnancy might justify interruption of early gestation despite adequate current cardiac reserve. The pathologic end result of this valvular healing process is too unpredictable, however, to warrant interruption after the fifth month of pregnancy. Future experience may have to alter this attitude.

Pregnancy should not alter the treatment of subacute bacterial endocarditis. Just as in the nonpregnant patient, it is important to determine the offending organism and its penicillin sensitivity, and render adequate dosage. The *streptococcus viridans* is the most common etiologic agent. Other organisms which occasionally cause subacute bacterial endocarditis are hemolytic and anhemolytic streptococci, staphylococci, *Hemophilus influenzae, Brucella melitensis* and others. Mixed infections also occur. Streptomycin is at present the antibiotic of choice for penicillin-resistant streptomycin-susceptible organisms.

Loewe and Eiber[15] recently reported eleven cases of clinically authentic subacute bacterial endocarditis (past history of rheumatic or congenital heart disease, fever, lassitude, weakness, anorexia, cutaneous or visceral embolization, and splenomegaly) in whom blood cultures were sterile despite repeated efforts. One case revealed organisms in the histopathologic sections at autopsy but no

organisms could be recovered from the thromboulcerative endocardial lesions. The authors conclude that cases with clinically authentic subacute bacterial endocarditis should be treated promptly and intensively, as though they had positive blood cultures. The diagnosis usually resolves itself within one week: if the patient has subacute bacterial endocarditis, there is appreciable clinical improvement accompanied by recession in temperature; if, however, the patient should have acute rheumatic fever (which presents the main diagnostic problem) the clinical manifestations remain static or may, in fact, become aggravated. Mention has already been made in this paper of two cases in which the diagnosis of subacute bacterial endocarditis was made clinically without positive blood cultures and penicillin started during pregnancy with subsequent cure. Both patients survived pregnancy and delivered living children.

Anticoagulant and antibiotic therapy have been combined in an attempt to decrease the incidence of embolic complications. Serious hemorrhagic manifestations have occurred (as in Case 5), and the end results of combined therapy have not been superior to those of antibiotic therapy alone. Labate[16] reported a case of antepartum thrombophlebitis treated with dicumarol for fifty-one days. The baby died in utero, and autopsy revealed massive mediastinal hemorrhage which could not be accounted for except by the dicumarol administered to the mother ante partum. Serious hemorrhage may result from disturbance of the normal clotting mechanism during labor and the early puerperium. The hazards of anticoagulant therapy at these times is apparent. Furthermore, Moore[17] has shown that the valvular lesions in subacute bacterial endocarditis are not of thrombic character, and he concluded that there was no pathologic basis for the use of anticoagulants in the disease.

Summary

There have been 10 cases with a diagnosis of subacute bacterial endocarditis complicating pregnancy in some 50,000 patients at the New York Lying-In Hospital from 1932 through 1947. The incidence of this complication is 0.02 per cent. Three cases with positive blood cultures occurred before the use of penicillin and all died during pregnancy or the puerperium. Seven cases treated with penicillin survived pregnancy and delivered normal living children. Two of the penicillin-treated cases had clinically authentic subacute bacterial endocarditis during pregnancy unconfirmed by positive blood cultures. Five of the penicillin-treated cases were proved by positive blood cultures: three had recently recovered from the disease prior to the pregnancy under consideration, and two developed the disease during pregnancy. The five proved cases are reviewed in an attempt to evaluate the significance of subacute bacterial endocarditis prior to and during pregnancy. An outline for the management of pregnancy, delivery, and the puerperium in rheumatic and congenital cardiac patients is given.

Conclusions

1. The past history of subacute bacterial endocarditis is not necessarily a contraindication to subsequent pregnancy. Pregnancy should be deferred until

the valvular pathology has resolved. The advisability of childbearing should then be determined by the current cardiac status, and accepted concepts of the management of the underlying rheumatic or congenital heart disease followed as outlined during pregnancy, delivery, and the puerperium. The type of delivery should be determined primarily on obstetric indications.

2. There is insufficient evidence to date, to suggest that the development of subacute bacterial endocarditis during pregnancy significantly alters this same management. Anticipation of delayed valvular damage may justify interruption of early pregnancy despite current adequate cardiac reserve.

3. Pregnancy does not alter the treatment of subacute bacterial endocarditis. The antepartum use of anticoagulants may endanger the fetus. Normal blood coagulation values should not be disturbed at the time of delivery or in the early puerperium.

4. The prophylactic use of antibiotics during labor and the early puerperium may prevent the development or recurrence of subacute bacterial endocarditis in patients with rheumatic or congenital heart disease.

The author is indebted to Dr. Curtis J. Becker of Staten Island, N. Y., for his cooperation in the management and delivery of CASE 1.

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FALLOPIAN TUBAL MOTILITY IN RELATION TO THE MENSTRUAL CYCLE

Clinical Study With Kymographic Uterotubal Insufflation

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THE hormonal activity of the ovary produces definite morphologic and functional changes in the uterus and Fallopian tubes. The effects on the uterine musculature and endometrium have been repeatedly demonstrated by many investigators. The relationship between the cyclic hormonal activity of the ovary and the functional state of the Fallopian tube in the human being has not been so clearly established.

Moreaux,[1] in 1913, investigated the changes occurring in the tubal mucosa of the rabbit. He found that the tubal mucous membrane was lined with ciliated epithelium during the sexually quiescent period. During the heat periods and early gravidity the ciliated lining of the tube was transformed into a secreting structure and the tubal lumen filled with granules of secretion. Structural changes of the same nature were demonstrated in the dog by Courrier and Gerlinger[2] and in the human tubal mucosa by Westman,[3] Snyder,[4] and others. The cellular transformation is controlled by the ovary and castration prevents these changes.

The spontaneous contractions of the uterine and tubal musculatures are also regulated by the ovarian hormones. In 1922, Blair[5] and Seckinger[6] independently demonstrated the cyclic activity in the musculature of the genital tract. Blair first observed this phenomenon in the excised uterus of the rat. Spontaneous contractions were slowest at estrus, the rate increasing gradually to a maximum in the resting stage. Wilson and Kurzrock[7] many years later established the normal pattern of human uterine motility in relation to the menstrual cycle. Seckinger studied the contractions of the excised Fallopian tube of the pig. He found uniform contractions occurred four to six times a minute except during estrus, when the contractions occurred ten to fifteen times a minute with alternation of groups of small and large excursions. The increased rapidity and large amplitude of contractions coincide with the time of Graffian follicle rupture and the passage of the ova through the tube. Studies in other species verify the relationship of ovarian function and spontaneous activity.

Uterotubal insufflation as a clinical test for tubal patency was introduced by Rubin[8] in 1920. It was not until 1925, however, that he obtained kymographic recordings of the tubal contractions. By this means, the functional activity of the intact Fallopian tube can be studied accurately in the human being as well as in the experimental animal. The correlation of preoperative kymographic tracings and the genital pathology demonstrated at the operating table and in the pathologic laboratory has greatly increased the value of the clinical test. The study of repeated kymographic curves in any given patient affords accurate knowledge of the functional state of the tube as well as a good impression of the pathologic conditions which may exist.

Using the technique of uterotubal insufflation, extensive studies have been made on the oviducts of the rabbit. The correlation of the rhythmic tubal contractions in relation to the hormonal state has been studied and the effects of various drugs have been demonstrated. Wimpheimer and Feresten[9] demonstrated the functional changes in castrated rabbits, rabbits primed with estrogens alone, and later with progesterone. Castration was followed by marked reduction in the frequency and amplitude of the tubal contractions. The contractions could be restored to normal patterns by the administrations of estrogens. Rubin and Davids[10] demonstrated the striking changes in tubal activity occurring with the administration of testosterone propionate. This hormone had an inhibiting effect on the tubal musculature, greatly diminishing its general tonicity and the amplitude of its contraction. The effects of Pituitrin, adrenergic and cholinergic drugs on the Fallopian tube in relation to the hormonal status was studied by Davids and Bender.[11] The hormonal state strikingly affected the tubal response to the various drugs administered.

In the human being, cyclic variations in tubal activity were found by Rubin,[12] using uterotubal insufflation clinically. Daily insufflations were undertaken by Sharman[13] on one patient throughout a menstrual cycle. He concluded from this case that there was no material change in the type of tracing obtained during any phase of the menstrual cycle. In this particular report, Sharman makes no mention of the correlation of the tubal activity with accurate knowledge of the ovarian activity by endometrial biopsy, vaginal smears, or basal temperature curves.

Methods

In the present clinical investigation, an attempt is made to correlate the Fallopian tubal activity in patients with normal ovulatory menses and patients who have repeated anovulatory bleeding. The effects of hormonal administration were studied in a number of cases. The patients were selected from those attending the sterility and endocrine clinics, where they had had comprehensive medical studies. Each case selected had essentially normal genitals, with no palpable uterine or tubal pathology. Basal temperature charts were kept accurately over a number of months by each subject. Repeated endometrial biopsies were performed, to determine the type of menstrual bleeding before and during the period of tubal study. The insufflation apparatus used was the standard Rubin model made by Becker.

All physical factors in the machine were kept constant throughout the tests. The gas was delivered under a pressure of 15 pounds and at a constant rate of flow of 60 c.c. of carbon dioxide per minute. The pressure and rate of flow were checked each day before starting any tests. The insufflations were performed by one person in order to eliminate any variations in technique and to establish satisfactory cooperation between patient and doctor. The cervix was exposed, cleansed, and painted with 3½ per cent iodine. It was then grasped with a tenaculum and a canula introduced into the cervical canal. A few moments were allowed to pass, until the patient was quiet and at ease, before the flow of gas was started. Proper air-tight obturation of the cervix was obtained by slight pressure of the rubber acorn tip of the canula against the cervix and slight traction upon the canula. Care was taken not to displace the uterus from its normal position in the pelvis. Such a procedure can possibly

stretch the mesosalpinx and tube, giving anomalous kymographic tracings. The insufflation was performed for five minutes or more at each test. The patients were insufflated every other day, starting within a day or two after the cessation of the menses. An endometrial biopsy was taken on the first day of flow of the following menstrual period. Each case was followed throughout an entire menstrual cycle and, in many cases, through two successive menstrual cycles. Certain patients with ovulatory menses were selected to determine the effect of estrogens on the tubal contraction patterns. Several patients with repeated anovulatory menses were used to test the reaction to the administration of combined estrogens and progesterone.

Material

Twenty patients with regular menses, on whom repeated endometrial biopsies revealed a secretory endometrium, were studied. The basal temperature curves exhibited characteristic temperature rises with persistent elevation of temperature until the onset of the succeeding menses. After studying the consecutive kymographic tracings obtained over the course of the menstrual cycles, certain facts became apparent. The initial pressure at which patency of the tube occurs shows marked variations from case to case in patients with normal genitals and normal menses. In individual patients the level of pressure at which patency occurs may be fairly constant throughout the cycle with only a difference of 10 to 20 mm. Hg throughout.

In other patients, the patency level occurred at times as low as 40 mm. Hg and on subsequent tests as high as 190 mm. Hg. There did not seem to be any consistent change of the tubal patency level with the time of the menstrual cycle. The majority of patients showed patency at levels between 40 and 100 mm. Hg. Of this group, only one case showed a consistently low patency level, which occurred between 10 and 30 mm. Hg throughout the test period.

The pattern of tubal contractions, that is, their frequency and amplitude, did, however, show interesting changes during the menstrual cycle. These patterns were not absolute, but occurred with sufficient regularity to permit of definite conclusions. During the first half of the menstrual cycle the contractions occurred with a frequency of four to five a minute and the amplitude of the contractions was 5 to 10 mm. Hg. During the mid-cycle, and approximately at the time of the elevation of the basal temperature, distinct changes in tubal motility were seen. The contractions appeared much less frequently, only one to three per minute, and the amplitude was greatly increased. The amplitude in some cases was increased from the previous 5 to 10 mm. Hg to levels as high as 50 mm. Hg, the average being 10 to 20 mm. Hg. This change of pattern was transient, lasting from one to two days. Following this, the contractions again occurred three to five times a minute with amplitudes of only 5 to 10 mm. Hg. The contractions were less regular and the base level of contractions was usually somewhat lower than during the early phase of the cycle. The general pattern of contractions showed no remarkable change from that of the early phase. (Fig. 1.)

Five patients whose menses were irregular and on whom repeated endometrial biopsies revealed proliferative endometrium were studied. Their basal temperature curves showed no characteristic changes such as are associated with the ovulatory cycle. These patients were insufflated in the same manner as the previous group. The average pressure level of tubal patency was somewhat lower than that found in the normal ovulatory group. Patency was estab-

lished usually between levels of 20 to 50 mm. Hg. The patterns of tubal contractions showed no significant change throughout the entire menstrual cycle. The contractions occurred four to five times a minute and their amplitude was 5 to 10 mm. Hg. The kymographic tracings from day to day were quite similar. As a group, the base level at which contractions occurred was lower than that of the normal ovulatory group. In one case, tubal contractions were absent throughout the test period. This case will be more fully discussed later. (Fig. 2.)

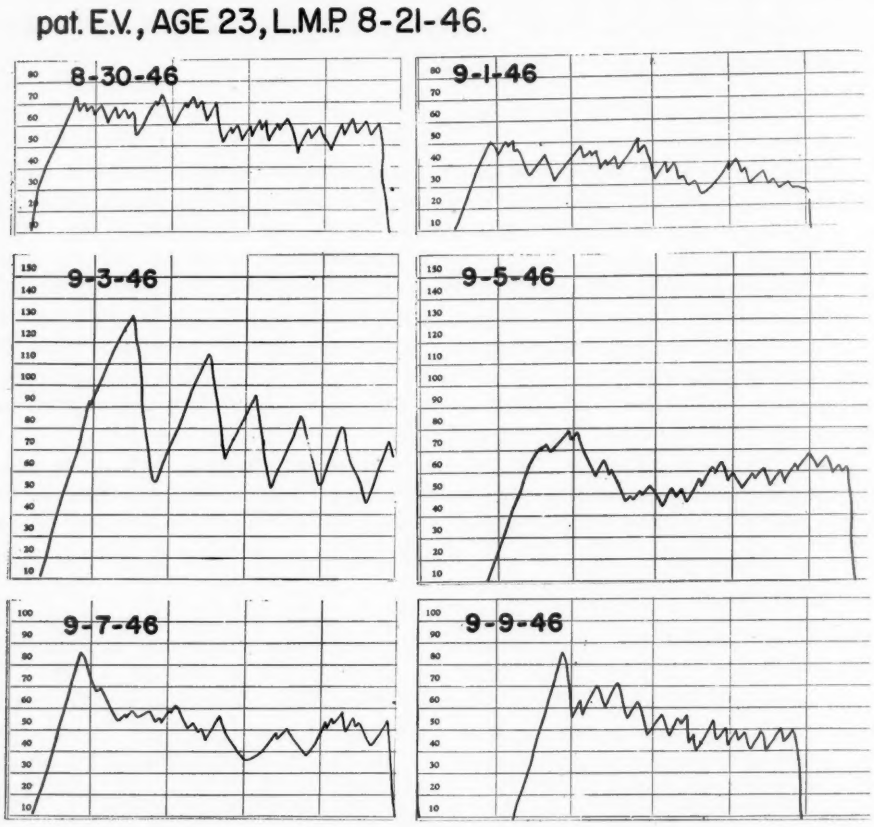

Fig. 1.—Above are six of the eleven consecutive tubal insufflation curves obtained on a patient during a normal menstrual cycle. These curves were obtained on the 10th, 12th, 14th, 16th, 18th and 20th days of the cycle. A marked change in tubal motility is seen on the 14th day of the cycle (9-3-46) which coincided with a distinct rise in the patient's basal temperature curve. Endometrial biopsy on the first day of the menses revealed a secretory endometrium.

The effect of estrogens on the pattern of tubal motility was studied in five women with normal ovulatory menses and in three women with anovulatory menses. In the latter cases, estrogens alone and in combination with progesterone were given. Stilbestrol was given in doses of 1 mg. daily and, in some cases, increased to 2 mg. daily. In the five normally menstruating women, the stilbestrol was started on the tenth day following the onset of the menses. In four of these cases, there was no appreciable change in the character of the daily tubal pattern. In one case, however, a very striking alteration took place. This patient had been insufflated on ten occasions before the administration of stilbestrol. Tubal patency had been present at pressure levels between 70 to 120 mm. Hg during these tests and the tubal contractions were of a normal

pattern. After five days of medication, 1 mg. stilbestrol daily, the patency level rose to 180 mm. Hg and on the sixth day the pressure rose to 200 mm. Hg without establishing tubal patency. Over the next eight days, four tests were performed and each time the pressure elevation was 200 mm. Hg corresponding to that encountered in the case of closed tubes or marked uterotubal spasm. The patient had a normal period the day following the last test and stilbestrol was stopped. The endometrial biopsy revealed a secretory endometrium. Ten days after the cessation of stilbestrol administration, an insufflation test was again performed. Tubal patency was present at 80 mm. Hg and the pattern of tubal contractions was normal. Two repeated tests during this same month revealed patency at normal pressure levels with normal tubal motility. (Fig. 3.)

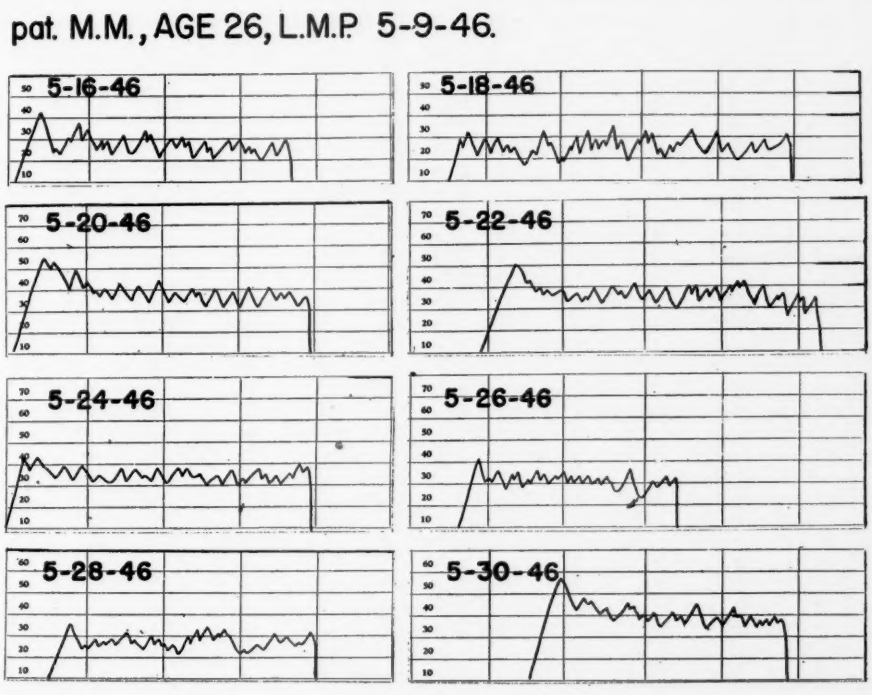

Fig. 2.—These eight consecutive uterotubal insufflation curves were obtained from a patient who had repeated anovulatory menses. The curves are quite similar from day to day. There is no marked change in motility on any day such as seen during the ovulatory mensus in Fig. 1. Endometrial biopsy performed on the first day of the menstrual flow revealed a proliferative endometrium.

In the three patients with anovulatory menses, 1 mg. of stilbestrol was given daily following the cessation of the last menstrual period. One patient showed no appreciable change in the tubal pattern throughout the test period. A second patient showed only a slight increase of 20 to 30 mm. Hg in the pressure level of tubal patency. The third case, however, exhibited a very marked alteration in the kymographic tracings. This patient had had eight insufflation tests performed before starting stilbestrol medication, 1 mg. daily. Tubal patency was present at 50 to 90 mm. Hg and tubal contractions were absent, the curve being a slightly irregular line. This type of tracing was present on all eight tests. After eight days of stilbestrol administration, insufflation revealed tubal spasm at 200 mm. Hg. This occurred on four subsequent tests and then was followed by a four-day menstrual flow. The endometrial biopsy revealed a proliferative endometrium. The stilbestrol was stopped at the onset of the menses.

Ten days later the insufflation test was repeated. Patency was present at 40 mm. Hg and tubal contractions were of normal character, the frequency being five to six per minute and the amplitude 5 to 10 mm. Hg. Seven subsequent insufflation tests revealed tubal patency at pressure levels between 20 and 60 mm. Hg and contractions remained regular at five to six per minute with amplitudes of 5 to 10 mm. Hg. (Fig. 4.)

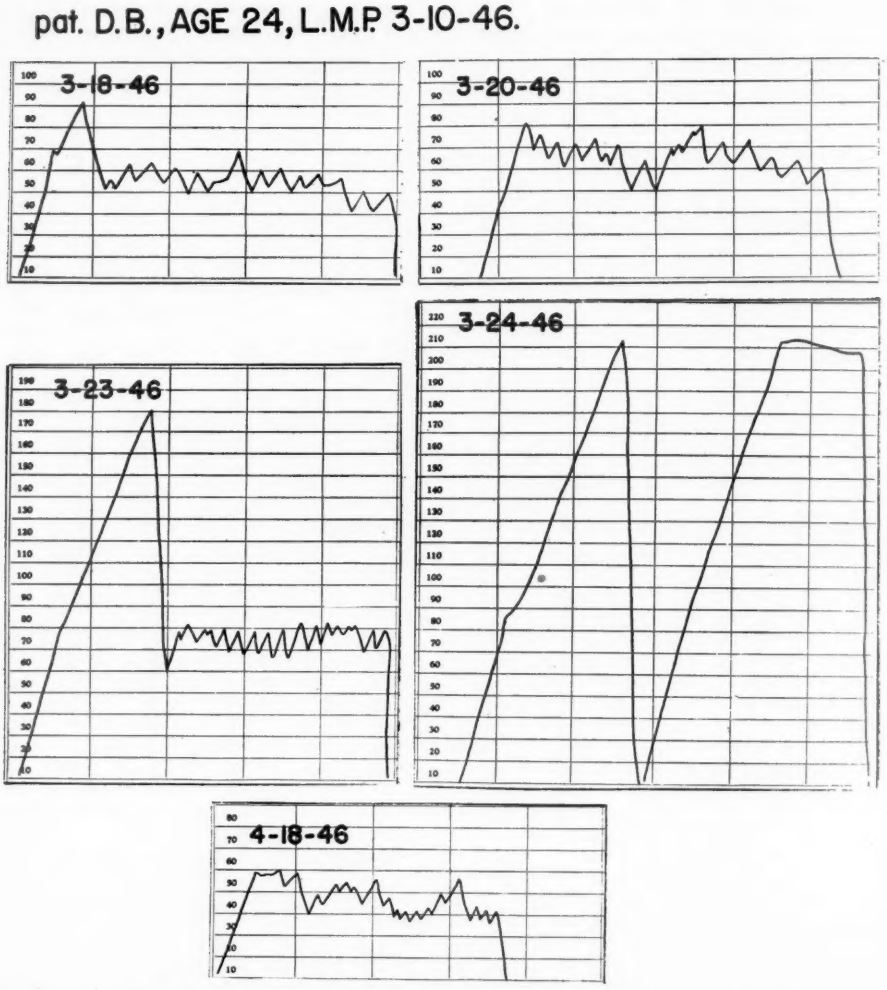

Fig. 3.—The above graphs demonstrate the effect of the daily administration of 1 mg. of stilbestrol to patient D. B., starting on the 9th day of her menstrual cycle. After five days (3-23-46) on stilbestrol, the tubal patency level rose to 180 mm. Hg. On the 6th day (3-24-46), patency could not be established at pressures as high as 210 mm. Hg. Four subsequent tests during the next eight days revealed nonpatency at pressures of 200 mm. Hg. Medication was stopped on the first day of the menses and ten days later (4-18-46) tubal patency was present at 60 mm. Hg and a normal pattern of tubal motility was present.

In three of the anovulatory cases, stilbestrol and progresterone were given in combination. The dosage was 1 mg. of stilbestrol daily in combination with 50 mg. of oral progesterone. Each patient received 10 mg. of progesterone by injection three times a week. In two of the three patients, the endometrial biopsies at the next menses revealed a secretory endometrium for the first time. In the third patient, the endometrium was still in the proliferative phase.

Despite the induced change in the endometrial structure in the two cases, there was no alteration in the character of the basal temperature curves and no striking alteration in the kymographic tracings of the tubal contractions.

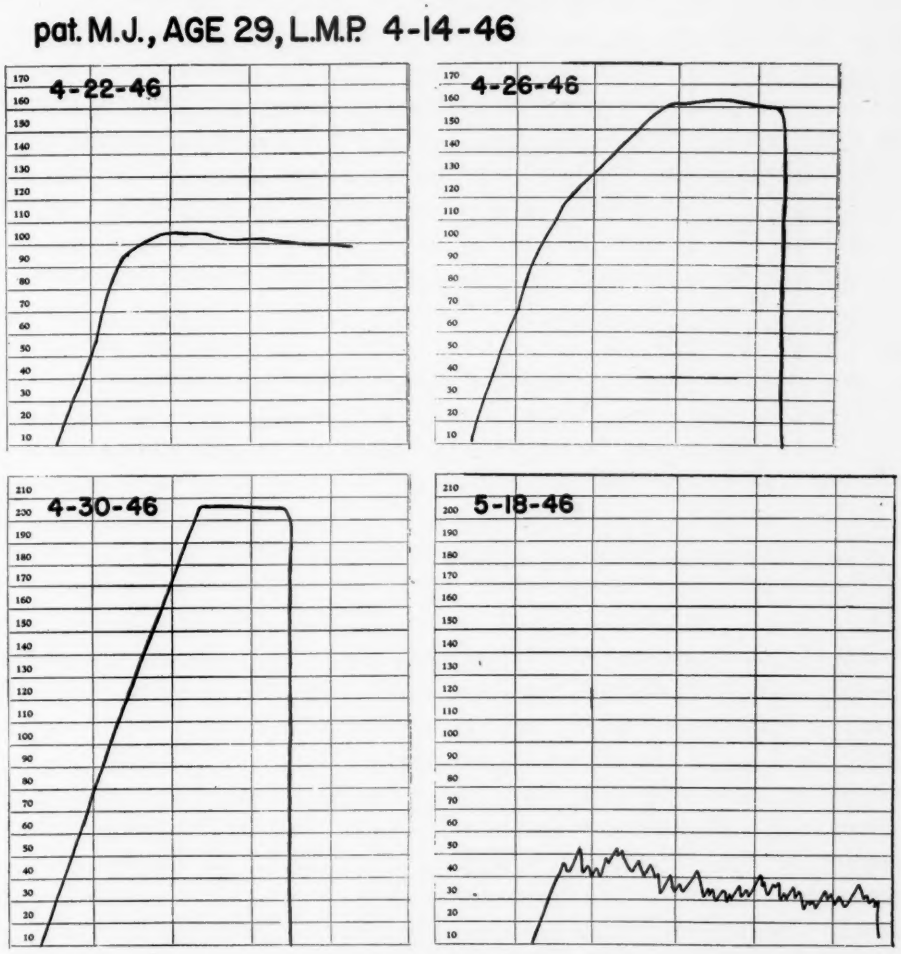

Fig. 4.—The above uterotubal insufflation curves demonstrate two striking effects of estrogen therapy. The graph of 4-22-46 shows no tubal contraction waves. This type of tubal curve was present on eight previous insufflations. Administration of 1 mg. of stilbestrol daily for four days produced a rise in the tubal patency level on 4-26-46 to 160 mm. Hg and in eight days (4-30-46) tubal patency could not be established at 200 mm. Hg. Ten days following the menses and the cessation of stilbestrol therapy (5-18-46) tubal patency was established at a pressure of 45 mm. Hg and tubal contractions of a normal pattern were seen for the first time.

Comment

The comparison of the consecutive kymographic records in the two groups of patients studied definitely establishes a difference in their functional state during the menstrual cycle. The one striking difference is that seen during the period at which we believe ovulation takes place. It is at this time, for one to two days, that the contractions of the Fallopian tubes become slower and of much greater amplitude. There is no such activity seen in those cases in which anovulatory menses occur. This change in tubal motility is probably

not entirely controlled by the hormonal activity of the ovary. It may be induced by a physicochemical reflex to the actual process of the rupture of the ovarian follicle and the passage of the ovum through the peritoneal cavity and Fallopian tube. In the absence of ovulation, the slow contractions of large amplitude do not occur. In the patient with anovulatory menses, the artificial stimulation of the Fallopian tubes by sufficient estrogens and progesterone to produce a secretory endometrium does not produce alteration of the tubal motility to resemble that seen at ovulation in the normal patient. It is also of interest that the basal temperature curves were not affected by the administration of the hormones in such combination as to produce a secretory endometrium. The pattern of motility of the Fallopian tube and that of the uterus through the menstrual cycle show distinct differences. Except for the short period following ovulation, the tubal motility of the early and late phases of the menstrual cycle are not very dissimilar. The uterus, on the other hand, develops two distinct patterns of motility. The contractions of the early phase of the cycle being rapid, four to five per minute and of low amplitude, while the latter half of the cycle is characterized by slow large amplitude contractions occurring once or twice a minute. These slow high contraction waves persist throughout the entire luteal phase of the cycle and do not seem comparable to the large slow contractions which occur in the Fallopian tube for so short a time during the period of ovulation.

The response of the individual patient to the administration of normal doses of a drug or hormone shows great variation. This is clearly demonstrated by the two cases of the eight so treated in which 1 mg. of stilbestrol produced an elevation of pressure up to 200 mm. Hg. Whether this was due to increased sensitivity and spasm of the tubal musculature alone, or possibly also to an actual obstruction of the tubal lumen due to proliferation of the tubal mucosa, one cannot say. However, where hormones are used as a therapeutic agent in sterility, it would probably be wise to determine if the patient is having an abnormally sensitive tubal response, as was seen in the two patients discussed. Theoretically, such a response would be detrimental to the normal passage of the ovum through the Fallopian tube. In one of these cases, the kymographic tracings revealed tubal patency but a complete absence of tubal contractions. After a short period of estrogen therapy, tubal obstruction was present on repeated tests until the medication was stopped. Following the next menses, tubal patency was present and contractions assumed a normal pattern for the first time. This patient had been under observation since 1941 and at no previous time did she exhibit normal tubal motility. Rubin[12] and White[14] have suggested estrogens as a therapeutic measure in cases with permeable strictures of the tubes, with the hope that such a response might occur.

It is of interest to note that in this group of twenty-five patients repeated insufflations produced no untoward reactions. Two of the patients became pregnant within two months after the studies were terminated. One was insufflated twenty times and the other eighteen times. It has been our feeling

that the passage of carbon dioxide through the Fallopian tube, even in such frequency as occurred in this study, will not induce any abnormal change in the endosalpinx.

Summary and Conclusions

1. Twenty-five patients were subjected to repeated tubal insufflations throughout one to two menstrual cycles and the type of menses determined by endometrial biopsies and basal temperature charts.

2. Patients with normal ovulatory menses exhibit slow large amplitude contractions at the time that ovulation is presumed to occur. The patterns of tubal contractions at all other times during the menstrual cycle are quite similar.

3. The patterns of tubal motility in patients with anovulatory menses are similar throughout the menstrual cycle. No such changes occur as are seen in the ovulatory cycle.

4. The administration of estrogens did not materially affect the pattern of tubal contractions except in two cases. In these two cases, the estrogen therapy produced obstructive pressures to 200 mm. Hg until the hormone therapy was stopped.

5. Repeated uterotubal insufflation with carbon dioxide did not produce any untoward effects. Two patients became pregnant shortly after having been repeatedly insufflated, in the one case twenty times and the other eighteen times.

6. Comparison of the tubal and uterine contractions throughout the menstrual cycle reveals that they do not conform to the same patterns of motility.

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FAILURE OF PROSTIGMIN TO AFFECT UTERINE BLEEDING IN THE RHESUS MONKEY

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THE so-called prostigmin test for pregnancy has attracted considerable attention in recent years because of its simplicity and the high rate of success attributed to it. There are now on record dozens of reports which include hundreds of cases in which the drug has been used in the treatment of women with amenorrhea. Yet there has been reported no study of the effect of prostigmin on menstruation under controlled conditions.

The apparent ability of prostigmin to induce menstruation in the nonpregnant woman with delayed bleeding is of great interest to the student of menstrual phenomena. In the laboratory, menstruation has been induced in animals only by oophorectomy, transection of the spinal cord, and hormone withdrawal in castrates. If prostigmin is effective in initiating the breakdown processes of endometrium which result in menstruation, its mode of action is certainly diametrically opposite to that of the steroid sex hormones whose effect in producing bleeding is manifest only when they are withdrawn. Furthermore, the duration of action of prostigmin is relatively brief, and it must be assumed that its administration initiates a chain of events which completes itself without further stimulus. As will be indicated, we are at present without any information as to how this phenomenon, if it exists, may occur.

In clinical practice, the patient who complains of amenorrhea is studied to rule out the presence of general disease, either nonspecific or endocrine in nature, or local pelvic pathology which might account for the complaint. She is then given prostigmin methylsulfate hypodermically, generally 0.5 to 1.0 mg. in the form of a 1:2000 solution, once a day for three days. If this regime is not followed by menstrual bleeding, the patient is presumed to be pregnant.

So little is known of the pathogenesis of amenorrhea in women, once general disease, pelvic pathology, and pregnancy are ruled out, that there is no accurate way of reproducing the condition in the laboratory. The rhesus monkey, whose menstrual cycles in the fall, winter, and spring average twenty-eight days in duration, normally develops amenorrhea during the summer months. In the absence of any other evidences of torpor, the animals tend to have prolonged intervals in the late spring and usually cease bleeding altogether in June, July, and August. In September, or occasionally in October, the cyclic pattern of menstruation is resumed. The color of the sex skin fades during this summer amenorrhea, indicating a decreased level of estrogenic substances, but it does not fade to the extent seen in castrates. The earliest attempts to induce bleeding in

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monkeys with prostigmin were naturally undertaken in these spontaneously amenorrheic animals, whose condition is at least analogous to that seen in the human being. When these attempts produced no reliable evidence of prostigmin effect, attention was turned to the possibility of affecting hormone withdrawal bleeding in castrate animals with prostigmin.

Castrate rhesus monkeys, given adequate doses of estrogens for a week or longer, will respond to the cessation of this therapy with uterine bleeding of three to seven days' duration which begins five to seven days after the last dose of hormone. The minor variations in the bleeding response depend on the size of the dose, the duration of treatment, and the volume of injected material, but with any single regime of hormone administration, the time of onset of bleeding and the duration of bleeding fall within narrow limits. If, in addition to a priming course of estrogens, a course of adequate doses of progesterone is given, bleeding follows the withdrawal of that hormone within two to three days, and lasts four to six days. The variation with this regime is less than that with estrogens alone. If a full priming course of estrogens and progesterone is followed by large doses of estrogens alone, bleeding does not ensue until after cessation of the estrogens, at which time it conforms to the pattern expected if progesterone had not been given at all. This variety of patterns of hormone withdrawal bleeding in castrate animals then offers an opportunity to investigate further the possible effect of prostigmin in initiating menstruation. The effects without prostigmin are known. If prostigmin in any way influences the process of endometrial breakdown and desquamation, it might be expected to alter the pattern or time relationships of withdrawal bleeding. Despite the fact that these conditions do not reproduce human amenorrhea, it appears worth while to report that, under these controlled conditions, there is no evidence of any effect of prostigmin on uterine bleeding in the rhesus monkey.

Materials and Methods

The animals employed in this study were mature healthy female specimens of Macaca mulatta in the colony of the Department of Embryology of the Carnegie Institution of Washington, in Baltimore.

Throughout the experimental periods, the animals were examined for the presence of bleeding by daily vaginal lavage.

Prostigmin methylsulfate* was administered intramuscularly in the thigh in doses of 0.38 mg. (0.75 c.c. of a 1:2000 solution) except in the few instances noted. The drug was administered on three successive days except when an animal was found to be bleeding on a day when a dose was scheduled; in this event the prostigmin was omitted.

Amniotin† was administered intramuscularly in the thigh in corn-oil solution. No special effort was made to keep the amount of injected solution constant. Except for the experiments employing massive doses, in which 0.5 c.c. of corn-oil solution was used, the amount administered daily did not exceed

*The Prostigmin employed in this study was generously supplied by Hoffmann-LaRoche, Inc.

†The Amniotin in oil and progesterone in oil employed were generously supplied by E. R. Squibb and Sons.

0.2 c.c. Progesterone[2] in corn-oil solution was given in the same manner, the largest single daily dose being 0.2 c.c.

At least four animals were used in each experiment in the series of hormone withdrawal studies. While all animals in any one experiment received identical doses of hormones, approximately half of the group received prostigmin in addition at one time, and the remainder at another. In this way, variables, such as changes in diet in the colony, climatic conditions, and differences in handling, are minimized and significant results can be obtained with relatively small numbers of animals. Since the results have all been negative, the experiments have been lumped together for the purpose of presenting the data in summary form.

Observations

A. *Prostigmin During Amniotin Administration.*—Three castrate animals were given approximately 400 International units of Amniotin per day for twenty days. Prostigmin was given in the middle of this course of Amniotin, but in no case did bleeding occur until after withdrawal of the hormones.

Five castrate animals were given 25,000 International Units of Amniotin daily for twenty-six days, as 0.5 c.c. of a 50,000 International Units per c.c. solution. In addition, prostigmin was given on days 21, 22, and 23 of the course of hormone injection, but bleeding did not result until after hormone withdrawal.

B. *Prostigmin Following Amniotin Administration.*—Eight castrate animals were given approximately 400 International Units of Amniotin daily for periods ranging from eight to nineteen days in a series of nineteen experiments. In twelve instances, prostigmin was given daily for three days beginning the day after the last dose of hormone. The time of onset of bleeding was scattered from the fourth to the eighth day after Amniotin withdrawal. The greatest delay was seen in two prostigmin-treated animals, the least in one not treated with prostigmin. In general, there was no difference between the experimental and control animals in regard to time of onset or duration of bleeding.

Five other castrates were given 25,000 International Units of Amniotin daily for twenty-six days and two of them were given prostigmin on days 27, 28, and 29. The time of onset and duration of bleeding was the same in the prostigmin-treated animals as it was in the three controls.

C. *Prostigmin Following Amniotin-Progesterone Administration.*—Fourteen castrate animals were given approximately 400 International Units of Amniotin daily for ten days and then approximately 200 International Units combined with progesterone increasing in amount from 0.5 to 1 mg. daily for ten to twelve days. Seven of these animals were given prostigmin on each of the three days following complete hormone withdrawal. There was no significant effect on the time of onset of bleeding.

D. *Prostigmin Following Amniotin-Progesterone-Amniotin Administration.*—All the animals in this group of castrates were given approximately 400 International Units of Amniotin daily for ten days and gradually decreasing doses thereafter for the next ten days, down to a daily dose of 150 International Units. During the second ten days, while Amniotin dosage decreased, progesterone in doses gradually increasing from 0.5 to 1 mg. was given. On days 21 through 26, four animals received 10,000 International Units of Amniotin daily, four others 5,000 International Units and the remaining four 1,250 International Units. Bleeding did not occur in these animals until several days after the withdrawal of all hormone administration, despite the fact that two animals in each group were given daily doses of prostigmin on days 21, 22, and 23, and

the other two on days 28, 29, and 30. There were no differences in time of onset or duration of bleeding between the prostigmin-treated and prostigmin-untreated animals after hormone withdrawal.

E. *Prostigmin During Spontaneous Amenorrhea in Intact Animals.*—Twenty-two animals with varying periods of amenorrhea, ranging from 29 to 112 days since the onset of the last menstrual period, were given the routine course of three daily doses of prostigmin.

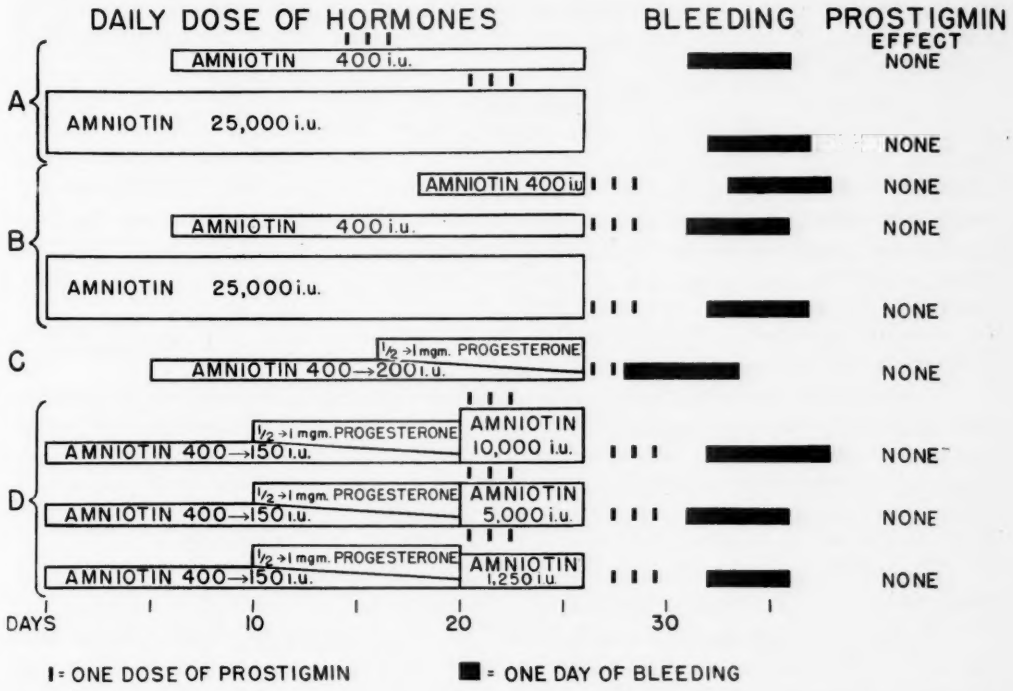

Fig. 1.—Chart of experiments designed to demonstrate prostigmin effect on hormone withdrawal in the rhesus monkey.

Experiments are grouped together as they are in the text and lettered correspondingly on the left margin of the chart. For economy of space, the days of prostigmin administration are indicated by vertical lines in relationsh p to each hormone regime. However, in each instance, equal numbers of animals did and did not receive the prostigmin on those days, whereas the hormone regime was the same for all in any group. The statement "None" under the heading Prostigmin Effect therefore indicates that there was no difference between the animals which did and those which did not receive prostigmin in time of onset or duration of uterine bleeding.

One group of ten animals, amenorrheic from 56 to 112 days, were given prostigmin in mid-May. One animal died of incidental causes during the experimental period. Of the remaining nine, seven did not bleed in the two weeks following prostigmin treatment. One animal bled, beginning on the day after the first dose of prostigmin, the 104th day since the last period. The other animal began to bleed on the 8th day after prostigmin was begun, the 86th day since the last menstrual period. None of these animals was pregnant.

A second group of animals was treated with 0.25 mg. daily doses of prostigmin in July. These animals had not bled for 29 to 38 days since the onset of the last menstrual period in June which, in each case, represented a greater lapse of time than was usually observed in that animal. Four of these animals bled, one on the second day and the other on the third day after completion of the course of prostigmin. In one of the latter animals only one day of bleeding was observed. None were pregnant.

A final group of five animals was studied in September, following amenorrhea lasting 48 to 80 days. One of these began bleeding on the second day of prostigmin administration, which was the 49th day since the onset of the last menstrual period. The other four animals did not bleed and were not pregnant.

F. *Saline Administered During Spontaneous Amenorrhea in Intact Animals.*—Seven intact animals, amenorrheic for periods from 39 to 66 days, were given 0.75 c.c. of normal saline solution on three successive days. One animal had a period of bleeding beginning nine days after the last dose of saline. The other animals did not bleed in the two weeks following the saline injections and were not pregnant.

G. *Summary of Experiments.*—Seventy experiments on castrate animals receiving hormone stimulation were carried out. Prostigmin did not induce bleeding during administration of Amniotin. When prostigmin was given following courses of Amniotin or Amniotin and progesterone, it did not accelerate or delay the expected hormone withdrawal bleeding. When given during courses of large doses of Amniotin which had followed Amniotin-progesterone priming, prostigmin did not induce bleeding, and when given after these courses of large doses of estrogen were stopped, it did not accelerate or delay the onset of bleeding. At no time did the administration of prostigmin prolong or shorten the period of bleeding.

Twenty-one experiments on animals in the process of spontaneous amenorrhea were performed. In only one group of animals, those treated in July after brief periods of delay in menstruating, did any considerable number of animals bleed following prostigmin administration. Two other animals, with more prolonged periods of amenorrhea, bled on the day after the first dose of prostigmin. None of the other animals responded to prostigmin with bleeding.

The administration of saline solution did not induce bleeding in a group of seven animals with varying periods of amenorrhea.

The dose of prostigmin employed in these experiments, 0.38 mg. or 0.75 c.c. of 1:2000 solution, is equivalent by body weight to ten to twenty times the recommended dose range for the human subject, 0.5 to 1.0 mg. With this dose a number of the animals exhibited gross muscle fibrillations within ten minutes after injection, lasting fifteen to twenty minutes. No animals became seriously ill and no serious effects were observed. Prostigmin was given in these large doses approximately 225 times.

Discussion

The prostigmin test for pregnancy was first reported by Soskin, Wachtel, and Hechter in 1940.[15] They based the use of prostigmin on the cholinergic concept of the action of estrogens on the endometrium[7] and on the hypothesis that the failure of the patient with a previously normal menstrual history to menstruate, in the absence of general disease of a nonspecific or endocrine nature, or pelvic pathology, or pregnancy, was due to a failure of the vascular supply of the endometrium. It was argued that inasmuch as estrogens were supposed to produce hyperemia of the endometrium by their cholinergic properties, the administration of a cholinergic drug should correct this vascular failure. They stated that: "In view of the large proportion of the estrous phenomena in animals which is dependent on hyperemia, it seemed likely that the role of hyperemia was probably even more important in the periodic menstrual bleeding in the human female. Considering the mechanism of this hyperemia, it would

presumably be under the influence of at least the parasympathetic nervous system.'' There are, however, so many unproved assumptions in this line of reasoning that it is worth while to retrace the course of development of the concepts involved.

Pompen,[10] in 1933, reported that within a short period after the administration of estrogens to rabbits, he could observe vascular stasis and dilatation of the serosal surface of the uterus as seen through an abdominal window. He also stated, without presenting any details, that the intravenous administration of atropine prior to the estrogens prevented the hyperemia of this peracute reflex, and that therefore the action of estrogens was a parasympathetic reflex. Reynolds[11, 12, 13] later studied the effect of estrogen administration on the acetylcholine content of the uterus of the castrate rabbit and demonstrated a sharp rise during the period of Pompen's peracute reflex. Emmens and his co-workers[4] were unable to confirm Reynolds' results, but the nature of the method of determination of acetylcholine used by both observers is such that negative results are not necessarily significant. It may therefore be accepted that administration of estrogens causes a hyperemia and a rise in the acetylcholine content of the rabbit uterus. Soskin and his co-workers have apparently made the assumption that this applies in full to the endometrium and, indeed, to the endometrium of primates.

It has recently been shown,[8] however, that the hyperemic effect of estrogens on the endometrium of the rabbit, as observed in transplants of endometrium to the anterior chamber of the eye, cannot be prevented by atropine, regardless of time and dose relationships. Furthermore, stilbestrol, which in Reynolds' experiments, was not responsible for a rise in acetylcholine content of the uterus, nevertheless produces a definite hyperemia of the endometrium. Two conclusions stem from these observations. One is that estrogenic effect on endometrium of the rabbit is not cholinergic in nature. The other, which follows by exclusion, is that the increase in acetylcholine content noted in the rabbit uterus after estrogen administration is due to increase in the myometrium.

The other facet of the hypothesis of Soskin and his co-workers is the relationship of vasodilatation to menstruation in primates. The very extensive researches of Bartelmez,[1] Daron,[3] Markee,[9] and others have shown that menstruation is preceded, not by hyperemia, but by a period of ischemia and regression. Markee has shown that regression is under way for a considerable length of time before bleeding begins, and that bleeding is the last in the series of events by which the endometrium returns to a resting state. Hence the ''vascular failure'' that Soskin and his co-workers proposed to correct by administration of cholinergic substances can hardly be responsible for amenorrhea if the endometrium has previously undergone follicular or progestational development.

Prostigmin effects are transitory when the drug is given hypodermically. They are manifest in five to ten minutes and last for no longer than three hours. It is difficult to envisage the mode of action of prostigmin in inducing menstruation under these circumstances, especially when it is administered every

twenty-four hours in a single dose, unless it acts to initiate the processes of regression in the endometrium. If this is the case, then one injection should be as efficacious as three, and the latent period of effect should be much greater than that reported by Winkelstein[16] in his cases. On theoretical grounds, therefore, the prostigmin test for pregnancy can be accepted with serious misgivings if it can be accepted at all.

Virtually nothing is known of the effect of prostigmin on the reproductive systems of experimental animals. Fontana[5] reported a few experiments in the rabbit in 1941, and recently preliminary reports of studies in the rat have appeared.[2] With the exception of the studies herein reported, there have been no experimental observations on primates.

Nevertheless, the great mass of reports of the use of the prostigmin test for pregnancy, most of them frankly enthusiastic, cannot be ignored. A representative but incomplete bibliography of these reports is included among the references.[5, 6, 14, 15, 16, 17a-ab] The greatest majority of these reports consist of entirely uncritical and uncontrolled observations. For example, it is generally accepted that no known substance in therapeutic doses will induce bleeding in the normally pregnant woman. It is, therefore, not surprising that prostigmin does not do so either, yet such cases are counted as therapeutic successes. Despite the acknowledged irregularity of the human menstrual cycle, many patients who have reported themselves only one to five days delayed in the onset of menstruation have been treated and any subsequent bleeding counted as a therapeutic success. On the other hand, the patient who has previously had a normal menstrual history and now suffers amenorrhea of weeks' duration, if she is not pregnant, presumably has some serious reproductive disturbance. Many such patients have been treated with prostigmin without such essential laboratory studies as endometrial biopsy, and subsequent bleeding counted as a therapeutic success. The many instances of hysterical amenorrhea can be expected to respond well to any substitutive therapy; certainly prostigmin is no specific. However, when all such cases as these are weeded out of the reports, there remains a residuum of reports of cases which cannot be explained at the present on any basis other than the therapeutic effect of prostigmin. It is unfortunate that only two authors have included in their series of cases controls in whom placebos were used,[6, 14] and in neither report were enough cases included to allow significant conclusions to be reached.

Amenorrhea is a normal condition in the rhesus monkey during the summer months, while the cycles in the cooler weather are approximately as regular as in the human female. When prostigmin was given to these animals exhibiting spontaneous amenorrhea, no significant number of them responded with bleeding, with the exception of one group with amenorrhea of a duration which did not fall outside the range of periods for all animals in the colony at the time of the year when the experiment was done.

In view of the failure of prostigmin to influence spontaneous amenorrhea, it was felt that attempts to influence hormone withdrawal bleeding was justified. When no effects were noted with the usual courses of estrogens and estrogen-

progesterone withdrawal bleeding, the studies were extended to include experiments in which the ability of large doses of estrogens to prevent progesterone withdrawal bleeding was employed to produce a simulation of amenorrhea. It is conceivable that some potent source of estrogens in the human being may produce amenorrhea in women following corpus luteum regression in just this manner. However, prostigmin has no effect on animals treated in this manner, down to postprogesterone doses of 1,250 International Units of Amniotin daily.

In conclusion, it may be stated briefly that, in the rhesus monkey, prostigmin has failed to induce menstrual bleeding in spontaneously occurring amenorrhea and has failed to alter the time of onset or duration of bleeding following varying courses of hormone administration and withdrawal. Inasmuch as there is reason to believe that the drug has some effect in the human being, there is a definite need for a critical clinical study in human amenorrhea.

Summary

1. The experimental studies of endometrial response to estrogens do not support the cholinergic concept of their mode of action. Menstruation in primates is not dependent upon hyperemia. The supposed theoretical basis for the use of prostigmin in human amenorrhea therefore cannot be accepted.

2. Administration of prostigmin hypodermically to rhesus monkeys does not induce menstrual bleeding in spontaneously amenorrheic animals, nor does it induce bleeding during estrogen administration, nor does it alter hormone-withdrawal bleeding following courses of estrogens, estrogens-progesterone or estrogens-progesterone-estrogens.

3. The efficacy of prostigmin as an emmenagogue and as a presumptive test for pregnancy is without experimental or critical clinical verification.

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THE ROLE OF DELAYED GASTRIC EMPTYING TIME IN THE ETIOLOGY OF ASPIRATION PNEUMONIA

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IN THE study of the problem of postdelivery atelectasis and aspiration pneumonia following general anesthesia, it was noted that the incidence of vomiting during anesthesia was inordinately high in obstetric patients. However, there were many patients in whom a diagnosis of aspiration pneumonia was made and in whom there was no recorded incidence of vomiting during or following delivery. In other patients who had undergone prolonged labor, undigested food and unexpectedly large quantities of fluid material sometimes appeared in the vomitus. It was not unusual for undigested food to be returned eighteen to twenty hours after the last ingestion of food. It was also noted that patients with such residual food and fluid after long labor often had abdominal distention in addition to that caused by the gravid uterus. It is well known that digestion may cease when labor starts.[1] However, the impression was gained from experience with deliveries in homes, where little "analgesic" medication is used, that anesthesia was better tolerated by such patients and the incidence of vomiting was much less.

It seemed worth while, therefore, to investigate in a comparative fashion the role which the medicaments employed in various "analgesic" and amnesic regimes of obstetric practice might play in delaying gastric emptying time.

Method

Mongrel dogs of either sex were selected and trained by handling until they were able to lie quietly while restrained on an x-ray table. They were maintained on a stock diet of horse meat, milk, corn meal, and dog food pellets in such fashion that regular weight gains were almost universal. After a fast of eighteen hours, a meal of approximately forty Gm. of barium sulfate in 150 c.c. of water was passed through a stomach tube. Emptying time of the stomach was determined to the nearest half hour by serial x-ray plates. A tablet of cascara (0.3 Gm.) was given by mouth to each dog after the stomach had emptied to prevent accumulation of barium sulfate in the lower gastrointestinal tract. An interval of one week was allowed between each successive experiment on the dogs.

Control determinations of gastric emptying time were made twice initially and after every two or three studies of the effects of medications. Drugs were given subcutaneously one-half hour before intubation. The doses and combinations of drugs employed were designed to simulate those used for "analgesia" in obstetrical practice and are indicated in Table I. A ratio of 4:1 between the average human dose in mg./kg. and the canine dose per kg. was used to

TABLE I

DRUG	AVERAGE HUMAN DOSE GRAINS	AVERAGE HUMAN DOSE MG.	DOSE/KG. 60 KG. HUMAN MG./KG.	DOSE FOR DOGS MG./KG.	RATIO DOSES DOG/HUMAN	EFFECT ON DOGS
Amytal and Seconal	Vi	360	6.0	12.0	2:1	Usually ataxic. Slight quieting first two hours, then hyperexcitable.
	iii	180	3.0	6.0	SC/oral	
Scopolamine—1st dose	1/150	0.4	0.0067	0.025		
45 min.—2nd dose	1/200	0.3	0.005	0.02	4:1	Dogs quieted but neither sleepy nor ataxic.
1 hr. 45 min.—3rd dose	1/400	0.15	0.0025	0.01		
3 hr. 15 imn.—4th dose	1/400	0.15	0.0025	0.01		
4 hr. 45 min.—5th dose	1/400	0.15	0.0025	0.01		
Pentobarbital	V	300	5.0	13.4	3:1	As with Amytal + Seconal. Ataxia marked.
					SC/oral	Emesis and defecation postinjection. Subdued 3 to 4 hours. No ataxia.
Morphine	1/6	10	0.16	0.67	4:1	
Meperidine[1] (Demerol)	jss	100	1.6	6.7	4:1	Quieted very slightly. No ataxia.
AN 148[2] (Methadon)	1/12	5	0.08	0.34	4:1	Profuse salivation, 1 dog. Defecation post-injection.
				0.67	8:1	Salivation and defecation—all dogs postinjection. Slight ataxia. Very subdued.

[1]Meperidine (Demerol) was furnished through the courtesy of W. A. Curran of Winthrop Chemical Company.

[2]Methadon, 6-dimethyl-4-, 4-diphenyl-3-heptanone hydrochloride (AN 148), was furnished through the courtesy of Dr. L. E. Josslyn of Abbott Research Laboratories.

allow for the relative species difference in surface area. This procedure is based upon the principle that the metabolism of hypnotic drugs is related to the general metabolic rate of the subject and therefore to surface area and to species differences in surface area. In the instance of the barbiturates, an additional factor of 50 to 100 per cent less than the calculated oral dose was allowed because of the necessity of using a parenteral route instead of the customary oral route of administration. The final ratio for Amytal and Seconal was 2:1 and for pentobarbital was 3:1.

The studies with Methadon (6-dimethyl-4, 4-diphenyl-3-heptanone hydrochloride), also known by the designation AN 148,[2] were included because of the present interest in this drug as a prospective analgesic agent of clinical value.

Results

The characteristic appearances of the dogs following medication are summarized in Table I. The barbiturates had a slight quieting effect but the animals were uniformly ataxic as indicated by slipping, weaving, and bumping objects when led into the x-ray room. Within two to three hours after injection, the quiescence had given way to hyperexcitability, although some ataxia remained for a longer time. This reaction has been described by Quigley et al.[3] following the intravenous injection of pentobarbital. Morphine in the dosage used produced its initial symptoms, characteristic gastrointestinal effects of emesis and defecation from ten to fifteen minutes after injection. It was for this reason that intubation and deposition of the barium meal into the stomach were delayed until one-half hour after administration of all initial medications. The dose of scopolamine used was insufficient to prevent the initial gastrointestinal response to morphine. Scopolamine quieted the dogs but produced neither sleep nor ataxia. Meperidine (Demerol) produced a similar result.

Methadon has been stated to be a more potent analgesic than morphine.[2] In a dose of 0.34 mg./kg., Methadon quieted the dogs, but not as much as morphine in twice that dose. Salivation occurred in one dog and defecation in all. When the dose of Methadon was doubled, the attitude of the dogs resembled that produced by morphine and salivation and defecation occurred routinely shortly after injection. Ataxia was minimal in this group.

The normal range of gastric emptying time was from one to five hours; the average of 35 such control studies in the ten dogs, 3.2 hours. The averages for the particular dogs used in the study of each drug ranged from 2.9 to 3.2 hours. Normal gastric emptying times for this study were more rapid than the four and one-half to five and one-half hour averages found by Meek and Herrin[4] when they allowed dogs to drink or eat a meal containing barium sulfate and milk. The speed with which the stomach was filled initially may have accounted for the early stimulus to motility in our studies. In considering the effects of medication, the control performances of each dog were used as the base line for estimating the effects in that animal. Average figures for each study are also given in Table II.

Amytal and Seconal in combination (7 dogs) delayed the emptying of the stomach scarcely at all. Most determinations were within the upper limits of normal for each animal. Similarly, there was no delay following pentobarbital (7 dogs) with but one exception which will be discussed later. Meperidine (Demerol) caused a slight delay, or an emptying time within the upper limits of normal for 4 of 6 dogs. The other two were well within normal ranges. Morphine (6 dogs) produced a very definite delay in all except one. Methadon (An 148), in an average dose, caused a marked delay in one sensitive animal but only slight slowing in 3 of the remaining 5 animals. When the dose of

Methadon was doubled, the delay was quite pronounced in the 5 less sensitive dogs. Scopolamine in five divided doses, administered over a period of about 5 hours to 5 dogs, caused a definite and prolonged delay in 4. The tendency of scopolamine to prolong gastric emptying time was also demonstrable when added, according to the same divided dose regime, to average doses of morphine, meperidine, or pentobarbital. This effect was not as apparent with morphine, which in itself caused marked delay in evacuation of the stomach, but was more evident when combined with meperidine and most obvious with pentobarbital. When only two doses of scopolamine were used after pentobarbital, a delaying effect was observable in 2 of 3 dogs.

TABLE II. GASTRIC EMPTYING TIME IN HOURS FOLLOWING ANALGESIC MEDICATION

DRUG / DOG NO.	7	11	5	A3	25	A1	26	12	10	6	AVG.
Control	2.0	5.0		2.0	3.0	3.0	4.0	3.0	2.0	5.0	
	2.0	2.0	3.0	6.0	2.5	2.5	5.0	5.0	3.0	4.5	
	1.0	2.0	3.0	1.5	3.0	3.0	1.5				
	3.0	5.0	1.5	2.0			5.0				
	4.0	2.0									
	5.0	2.5									
AVERAGE	2.8	3.0	2.5	2.9	2.7	2.7	3.9	4.0	2.5	4.75	3.2
Amytal and Seconal	3.0	2.75	2.0	5.5	4.0		5.0			4.0	
	6.0	3.0	3.5								3.8
Morphine	14.0	8.0		10.5	6.0	6.0	5.0				8.3
Scopolamine × 5	5.0	8.0	5.5		9.0		10.0				
		10.0									7.7
	13.5+	13.5+	7.5					7.0	9.5		
Morphine + Scop. × 5	13.0+										10.1
	4.0	6.0	3.0	6.5	6.5		3.5				
Meperidine (Demerol)	6.5	4.5									5.0
Meperidine and Scop. × 5	13.5	9.0		12.0		6.0	8.0				
		9.0									9.7
	2.5	2.0	9.0	2.0	3.0	2.0	3.0				2.6
Pentobarbital (Nembutal)		4.0									(3.5)
	9.5	6.0	3.0								
Pentobarbital + Scop. × 2											
		7.0		8.0	5.5	7.0	7.0				6.9
Pentobarbital + Scop. × 5											
AN 148 (Methadon)											
0.34 mg./kg.	12.5	5.0		6.0	4.0	3.5	3.0				5.5
	8.0	8.0									
	13.0			3.0							
AN 148 0.68 mg./kg.		8.0		6.0	10.0	8.0	9.0				8.2

× = Number of doses.

One dog (No. 7) was very sensitive to the effects of morphine (emptying time 14 hours), morphine and scopolamine (13.0+ and 13.5+ hours) and Methadon (12.5, 8.0, and 13.0 hours). This animal showed the most severe depression and marked salivary and defecatory responses to the average dose of Methadon. A very active young dog (No. 11) that was studied 23 times in 9 months showed a very marked reaction to morphine and scopolamine. Another dog (No. 5)

had a characteristically rapid emptying time normally. The two seemingly paradoxical findings of emptying times of nine hours with pentobarbital and three hours with pentobarbital plus scopolamine for dog No. 5 perhaps can be related to the fact that it developed a pharyngeal abscess and died one week after the test with pentobarbital-scopolamine. However, no weight loss was observed until immediately before death.

Discussion

We have shown that in dogs certain analgesic or amnesic agents and combinations of such agents, in proportions commonly employed in obstetrics, may delay the passage of food from the stomach for a significant period of time. Such extension of time may vary from one to nine hours beyond the normal. Similar findings have been described previously for the individual drugs,[2, 3, 5, 6, 7] but the comparisons made here are somewhat different from those previously made.

The data presented may serve to re-emphasize the particular relationship which the smooth-muscle action of "analgesic" drugs has to the production and conduct of anesthesia for obstetric patients. Delay in emptying the stomach of food may be brought about by the emotional and physical strain of labor,[1] in synergism with the smooth-muscle actions of these drugs. We have reason to believe that delays comparable with those recorded in these experiments may occur in human beings. A total emptying time of from eight to fourteen hours would in many instances extend, if labor started shortly after eating, into the second stage of labor. Undigested food would remain in the stomach of this patient at the time when normally she would be induced into anesthesia for delivery. Oftentimes such residual food is augmented in volume by accumulated fluid and gas. Thus, within the already crowded abdominal cavity, the stomach and distended loops of bowel may occupy an inordinate amount of space.

Anesthetic management of such a patient with gastrointestinal distention may be complicated in one or both of two ways: (1) the attainment of an adequate concentration of anesthetic in the blood stream and brain may be difficult and slow because respiratory exchange may be diminished in the supine position by the pressure of the abdominal contents against the diaphragm and slow passage through the second anesthetic stage of heightened reflexes may lead to vomiting or to excessive accumulation of mucus; (2) regurgitation of small amounts of gastric fluid and undigested food may occur as from a bulb syringe, when the uterus is caused to compress the stomach. This is especially so if the patient is moved under anesthesia in such manner that the pelvis and abdomen are flexed upon the thorax. It is also true if pressure, exerted upon the fundus of the uterus to aid in the expulsion of the fetus, inadvertently is directed dorsally upon the distended stomach, instead of in the axis of the uterus. The premedicated, anesthetized patient is unprepared reflexly to guard against such regurgitation and the anesthetist is not warned by the usual reflex signs of vomiting that regurgitation has taken place. Aspiration into the trachea of regurgitated gastric contents might therefore occur in this crucial interval and the incipient effects of irritation by the acid material might not be very

evident until the anesthetic is discontinued and the patient begins to recover her reflexes. Upon recovery of consciousness the patient may complain of pain in the chest and often may cough up sputum which is blood tinged. The color of mucous membranes and nail beds may be cyanotic; the temperature, pulse, and respiratory rate may be increased.[8] Signs of respiratory difficulty, upon recovery of reflexes, may be out of proportion to any evidences of aspiration during the anesthetic procedure. Mendelson[9] has shown that the acidity of aspirated gastric juice is an important factor in the pulmonary reaction leading to aspiration pneumonia.

Several preventive measures may be suggested. It should be re-emphasized from this discussion how important it can be that the physician impress upon his patient the dangers and uselessness of eating after labor starts, especially if the use of sedative drugs is anticipated. Emesis may be induced in patients admitted to the delivery floor with a history of recent ingestion of food. The advisability of passing a Levin tube and decompressing the stomach should be considered in those patients whose abdomens become tense and tympanitic during labor and while under analgesic medication. This has been practiced on occasion with relief of discomfort for the patient, improved effectiveness of medication, and more rapid progress of labor. Restraint and care in moving anesthetized patients and careful application of pressure, if pressure is to be used upon the fundus of the uterus, must be practiced. Probably one of the soundest procedures in the management of the patient with accumulated gastric content, as well as the patient with an upper respiratory infection, is the avoidance of general anesthesia entirely, by the use of caudal or low spinal anesthesia for delivery. The patient with spinal anesthesia retains reflex protection against regurgitation.

Conclusions

1. Studies of gastric emptying time in dogs under treatment with analgesic or amnesic agents or combinations of agents commonly used in obstetrics were made employing an x-ray technique.

2. The barbiturates, Amytal and Seconal or pentobarbital (Nembutal) seemed scarcely to delay gastric emptying time at all despite the production of marked ataxia.

3. Meperidine (Demerol) and Methadon (AN 148) in average doses delayed the time slightly except in particularly sensitive animals.

4. Morphine, and Methadon in large dosage, produced a definite and marked delay in the passage of the test meal.

5. Scopolamine in five doses over five hours definitely prolonged the emptying time and when added to other medications added to their effects.

6. The relationship of the effects of medication to the incidence of vomiting and regurgitation under general anesthesia and to aspiration pneumonia is discussed.

The author wishes to acknowledge the technical assistance of Miss Peggy Howard and Miss Elizabeth Glassco in carrying out this study.

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2065 ADELBERT ROAD

AGE, INCIDENCE, AND DISTRIBUTION OF 4,652 CASES OF CARCINOMA OF THE CERVIX

With a Report of Three Cases During the First Two Decades of Life

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ONE of the important factors in the approach to the cancer problem is early diagnosis, which is largely in the hands of the family physician. It is imperative that he be familiar with the incidence of cancer in relation to the age of the patient.

An age study was therefore made of 4,652 patients with cases of carcinoma of the cervix admitted to the Roswell Park Memorial Institute during the years 1914 to 1946, inclusive. These cases comprise 15 per cent of all admissions to the hospital and 62 per cent of all malignant gynecologic admissions. During this period there were approximately 1,500 patients with carcinoma of the body of the uterus admitted to the hospital, about one-third of the number of cases of carcinoma of the cervix. Comparing the occurrence of carcinoma of the cervix with that of carcinoma of the body of the uterus, the ratio is 3 : 1.

The data of 4,652 cases of carcinoma of the cervix have been tabulated according to age distribution, as shown in Table I. The same data are shown graphically in Fig. 1, Curve A. This curve represents only the age at the time of admission of patients having carcinoma of the cervix; it shows a definite peak at the age of 47 years, but it must not be interpreted to mean that the peak of incidence of the female population as a whole is at the age of 47 years. In order to obtain the age incidence in a more representative manner, the data of Table I have been computed for the different age groups in relation to the female population of the State of New York (1940 census). These calculations are shown graphically in Fig. 1, Curve B.

The 4,652 patients with carcinoma of the cervix represent women from New York State admitted to the Roswell Park Institute during the years 1914 to 1946 inclusive, and do not represent all the cases of this type in the entire state. Nevertheless the number is a large one, and therefore it is considered to be fairly representative. From these data it can be concluded that carcinoma of the cervix does occur in any age period subsequent to the first decade and attains a maximum of incidence at the age of 57 years. It may be gathered that carcinoma of the cervix under the age of 20 years is exceedingly rare, but it does occur in an appreciable percentage of cases between the ages of 20 and 30 years as is shown in Table I, where 146 cases or 3 per cent occurred in this decade. Carcinoma of the cervix occurs three times as frequently after the age of 75 years as before the age of 25 years. Approximately 20 per cent of our cases occurred before the age of 40 years. About 60 per cent were found immediately preceding and including the average menopause age, between 40 and 60 years of age. It was still relatively

TABLE I. DISTRIBUTION OF CASES OF CARCINOMA OF THE CERVIX ACCORDING TO AGE AT ADMISSION

AGE	NUMBER ADMITTED	PER CENT OF TOTAL ADMITTED	FEMALE POPULATION N. Y. STATE CENSUS 1940	RATE PER 10,000*
15-19	2	0.05		
20-24	25	0.6	594,549	0.42
25-29	121	2.6	616,934	1.96
30-34	295	6.3	593,492	5.0
35-39	468	10.1	561,084	8.3
40-44	611	13.1	530,311	11.5
45-49	759	16.3	476,854	15.9
50-54	744	16.0	408,192	18.2
55-59	619	13.3	319,838	19.4
60-64	477	10.2	264,708	18.0
65-69	286	6.1	207,659	13.8
70-74	156	3.3	143,218	10.9
75-79	68	1.5	146,417	6.1
80-84	21	0.5		
	4,652			

*Rate of number admitted, calculated from columns 2 and 4.

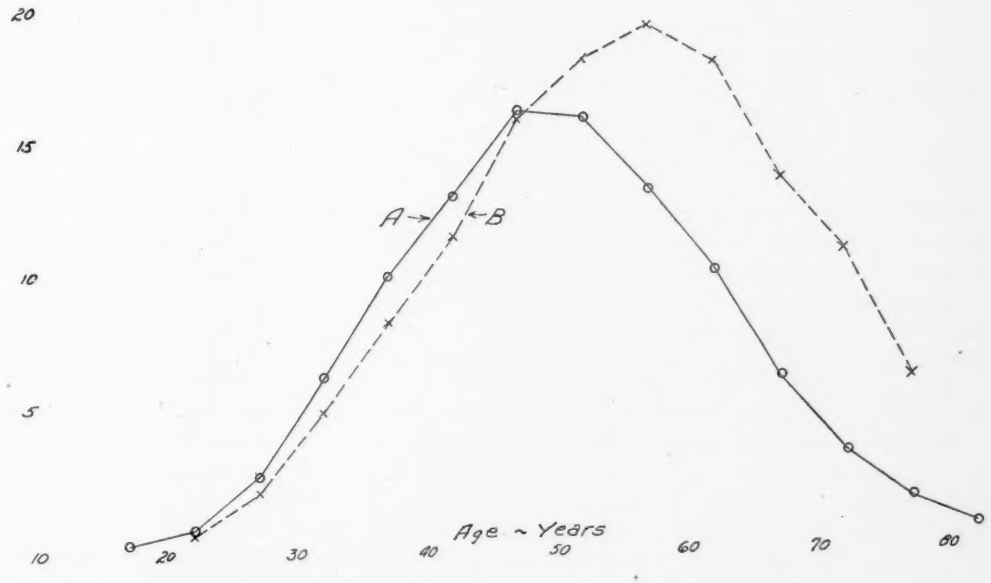

Fig. 1.—Showing the age distribution of 4,652 cases of carcinoma of the cervix.
0———0, age at admission, per cent of total.
X------X, age incidence per 10,000 of the normal female population of New York State, 1940 census.

common until the age of 65 years, after which there was a gradual decrease in the number. This decrease at first glance would lead one to suppose that it was due to the effect of the normal death rate after the age of 65 years. However, by referring to Table I, Columns 4 and 5, it is evident that while the female population is decreasing with increasing age, the rate of cancer incidence of the cervix is decreasing at a faster rate.

All the cases of carcinoma of the cervix were subdivided into their respective histologic classifications as shown in Table II. A plot of the ages

TABLE II. AGE DISTRIBUTION IN CARCINOMA OF THE CERVIX, 4652 CASES ACCORDING TO THE HISTOLOGIC CLASSIFICATION

AGE	SQUAMOUS CARCINOMA		ADENOCARCINOMA		ADENOACANTHOMA	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
15-19	2	0.045	0	0	0	0
20-24	25	0.57	0	0	0	0
25-29	117	2.7	2	1.2	2	1.6
30-34	283	6.5	4	2.4	8	6.6
35-39	450	10.5	12	7.4	6	4.9
40-44	586	13.4	16	9.9	9	7.4
45-49	717	16.4	24	14.8	18	14.9
50-54	700	16.0	29	17.9	15	12.4
55-59	574	13.1	22	13.6	23	19.0
60-64	437	10.0	20	12.3	20	16.5
65-69	256	5.8	18	11.1	12	9.9
70-74	141	3.2	8	4.9	7	5.8
75-79	63	1.4	4	2.4	1	0.82
80-84	20	0.45	1	0.62	0	0
	4369		162		121	
PER CENT OF TOTAL	94.0		3.4		2.6	

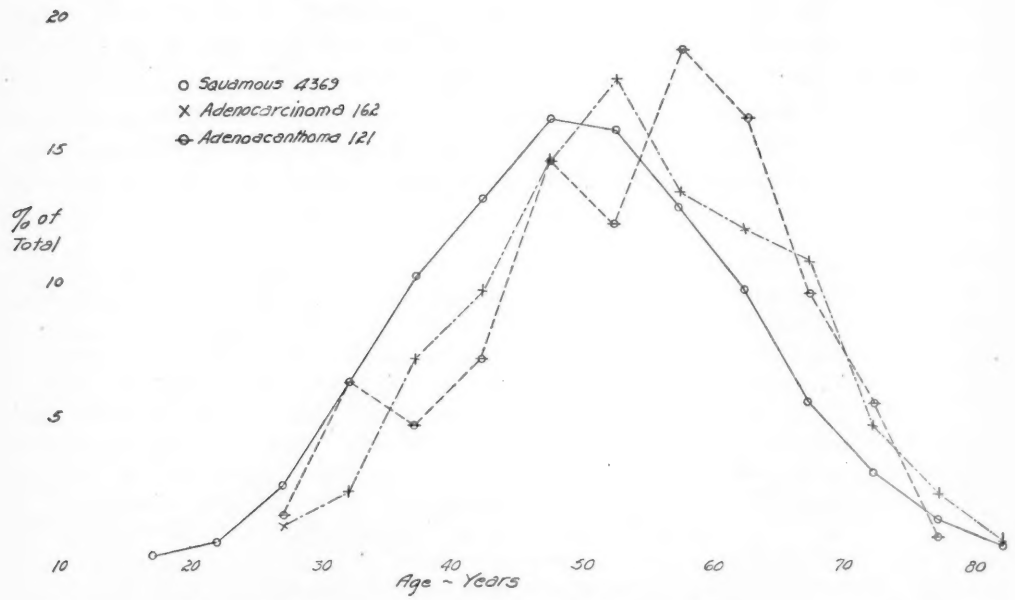

Fig. 2.—Showing the age distribution at the time of admission of the three histologic types of carcinoma of the cervix.

0———0, 4,369 cases of squamous cell carcinoma of the cervix.

X------X, 162 cases of adenocarcinoma of the cervix.

0------0, 121 cases of adenoacanthoma of the cervix.

at admission of the cases in these three groups is shown in Fig. 2. It is evident that the majority of the cases of squamous cell carcinoma occur approximately five years earlier than those of adenocarcinoma and adenoacanthoma, and reach a peak at admission at the age of 47 years. Adenocarcinoma occurs later in life, reaching a peak at admission at the age of 52 years, whereas adenoacanthoma shows two peaks, one at 47 years, and

the other 57 years. These two peaks may be due to the fact that there are comparatively few cases of adenoacanthoma in this series of cases, and therefore these peaks may not be statistically significant. On the other hand, they could signify that adenoacanthoma falls into two separate groups, depending on the location of the primary focus from which it is histologically derived, namely, either the cervix or the fundus. The reason for this observation is that the one peak at 47 years of age coincides with the peak of the squamous cell carcinoma of the cervix curve, and the other peak at the age of 57 years is identical with that which we have found to be characteristic of the fundus carcinoma cases.

Novak[1] states, "that there has been considerable discussion as to whether adenoacanthoma arises from a double matrix, or whether the squamous transformation is a later development in an adenocarcinoma." The later theory is the one which seems to have the widest acceptance, but apparently the former viewpoint is brought out by the curve in Fig. 2, with its double peak.

The age of the youngest patient is the squamous cell carcinoma series is 18 years, and that of the oldest is 84 years. The age of the youngest patient of the adenocarcinoma and adenoacanthoma series is 25 years, and the oldest is 83 years for the former and 79 years for the latter. There is a total of three cases in the first two decades of life, which are of particular interest in regard to the age distribution of carcinoma of the cervix. These cases are reported in detail as follows:

Case Reports

CASE 1.—L. P., aged 20 years, American-born married woman, gravida 0, was first seen in the clinic at the Roswell Park Institute on July 27, 1914. The patient had consulted her family physician one month prior to admission. She had been complaining of a watery discharge and irregular vaginal bleeding for the past two years. She began to menstruate at the age of 12 years; the menses occurred regularly every twenty-eight days and lasted for three or four days with moderate flow. There was no associated discharge or pain, and the menses appeared normal in all respects. At the age of 18 years she began to have intermenstrual bleeding and mild bloody discharge. She also had a sudden and profuse vaginal hemorrhage before entering the clinic. Pelvic examination revealed a fundus which was normal in size, the right adnexa were normal, the left adnexa showed a large, tender mass. The cervix was replaced by a large ulcerating cauliflower-type tumor mass. There was fixation in both broad ligaments. Biopsy of the tumor proved to be a squamous cell carcinoma of the cervix, Grade II (see Fig. 3).

This patient received a series of eight treatments of low voltage x-ray, using multiple ports to the pelvis and perineum, with no notable improvement. The patient died three months after admission, and an autopsy revealed multiple metastases to the lungs, liver, omentum, and pelvis. In retrospect, this case would be classified according to the League of Nations as a clinical Stage IV.

CASE 2.—G. A., 18 years of age, gravida iii, married five years, was first seen at the Clinic of the Roswell Park Institute on Aug. 11, 1931. The patient stated that she had been flowing excessively at frequent intervals for the past seven months. Her family physician saw her for the first time one month prior to admission to the clinic. No previous treatment had been given. Her periods began at 12 years of age and were regular, every four weeks with moderate flow, lasting five to six days. Her present bleeding she attributed to her last pregnancy which was seven months prior to admission. Pelvic examination showed an ulcerating, indurated tumor with involvement of the anterior

and posterior lips of the cervix and both broad ligament areas, as well as beginning infiltration of the rectum and base of the bladder. A biopsy showed a squamous cell carcinoma of the cervix, Grade III (see, Fig. 4). Clinically, she was a Stage IV. On Aug. 13, 1931, radon seeds were implanted into the cervix and radium tubes inserted into the uterine canal; total seeds and tubes were 5,140 millicurie hours. There was marked regression of the tumor during the next few months. On March 19, 1932, the patient was re-admitted, complaining of discharge and bleeding. Pelvic examination revealed a hard, nodular cervix, with pelvic infiltration. The patient again received seeds and tubes for a total of 4,500 millicurie hours, but improvement was negligible. The patient died of disease on Aug. 26, 1932. No autopsy was performed.

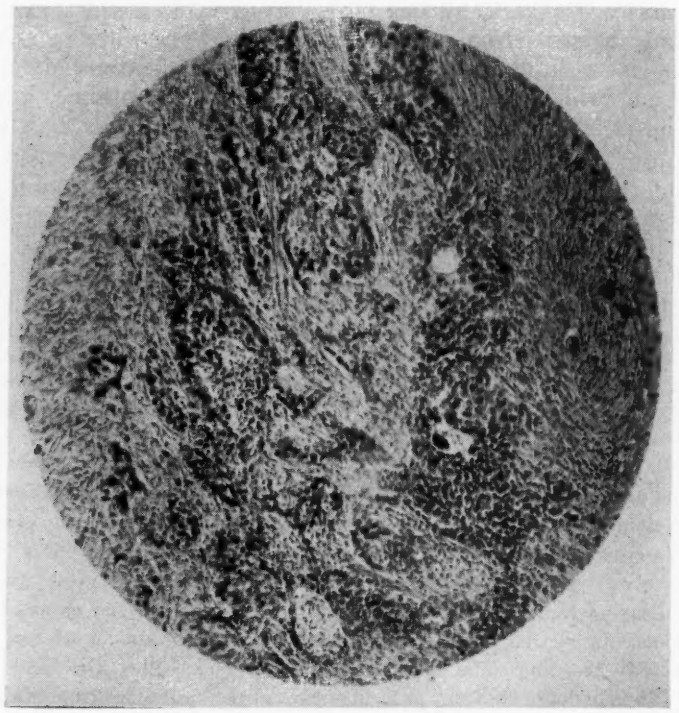

Fig. 3.—Case 1. Section of tissue from the cervix shows a squamous cell carcinoma. Some of the tumor cells are differentiated in character, but the majority are found to be anaplastic. This tumor was infiltrative in character. Diagnosis: Squamous cell carcinoma, Grade II plus.

CASE 3.—K. W., 20 years of age, gravida 0, married four years, was first seen at the clinic of the Roswell Park Institute on March 28, 1934. The patient stated that she had had a watery discharge for four years. Menstruation began at 13 years of age. The menses were always regular until the last period, at which time there was a heavy, steady flow persisting for one month previous to admission. Her family physician was consulted for the first time on March 21, 1934. She was referred here for treatment. Pelvic examination revealed a fungating epithelioma involving the whole cervix and extending onto the vaginal mucous membrane. It was classified as a clinical Stage II. A biopsy was reported to be a squamous cell carcinoma of the cervix Grade II (see Fig. 5). Treatment over a period of forty-eight hours consisted of radon seeds, radium tubes, and x-radiation, for a total of 8,338 r. The patient has been followed for the past thirteen years, and examination on March 13, 1947, revealed no evidence of disease.

The information contained in these reports is briefly summarized in Table III.

In reviewing the literature, we found that Pollack and Taylor[2] recently made a survey of all the reported cases of true carcinoma of the cervix which occurred during the first two decades of life. They composed a chart of thirty cases, and added one of their own, making

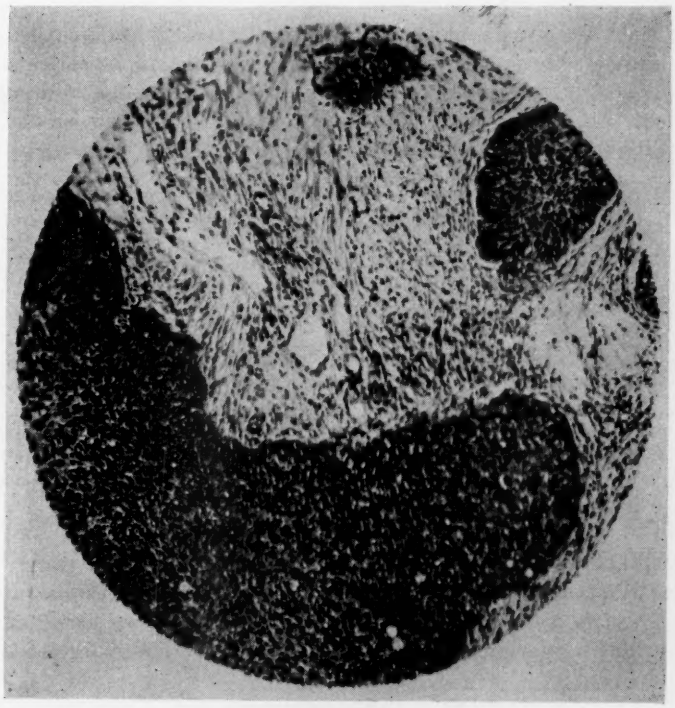

Fig. 4.—Case 2. Section of tissue from the cervix showing a squamous cell carcinoma. Tumor cells are anaplastic in character, and fail to show any degree of differentation. Diagnosis: Squamous cell carcinoma of the cervix, Grade III.

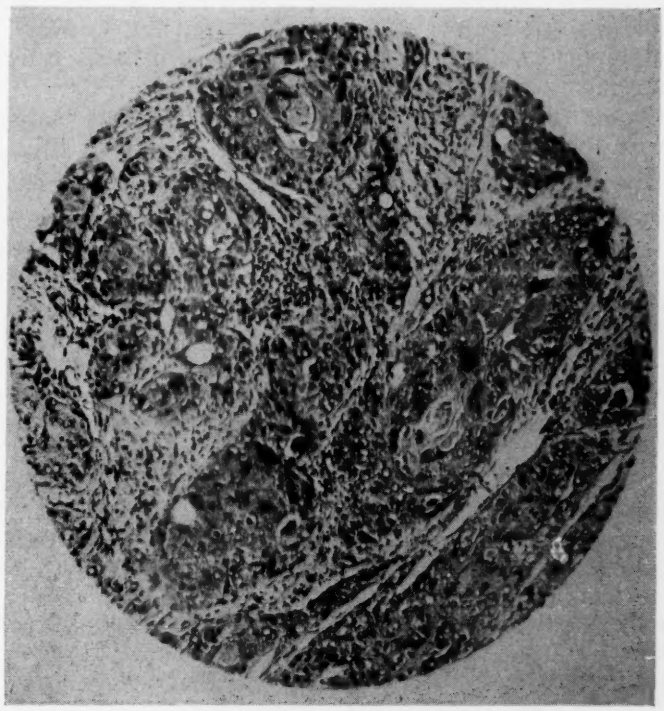

Fig. 5.—Case 3.—Section of tissue from the cervix shows a squamous cell carcinoma. As a rule the tumor cells are well differentiated in character with extensive keratinization and pearl formation. Some inflammatory reaction is found in the supporting stroma. Diagnosis: Squamous cell carcinoma of the cervix, Grade II.

a total of thirty-one. With those added in this report, the total has been increased to thirty-four. Of these thirty-four cases, twenty-two, or 65.7 per cent, were patients with adenocarcinomas; seven, or 20.6 per cent, were patients with squamous cell, and four, or 11.8 per cent, were not classified. The pathology of one patient showed both squamous and glandular features, and probably fell into the adenoacanthomous group. The relation between squamous cell carcinoma and adenocarcinoma of the cervix in this younger group is the reverse of that found in the group as a whole.

TABLE III. SUMMARY OF CASES 1, 2, AND 3.

CASE	HISTOLOGY	AGE (YEAR)	REMARKS	FIVE-YEAR SURVIVAL
1	Squamous carcinoma	20	Died of disease, 3 months, with multiple metastases. Treatment x-ray therapy	No
2	Squamous carcinoma	18	Died of disease, 1 year. Treatment radium therapy	No
3	Squamous carcinoma	20	Alive and well 13 years. Treatment radium and x-ray therapy	Yes

Of the thirty-four cases, there were five cases which survived five years. This represents approximately 15 per cent five-year survivals free of disease. While this survival is smaller than that for the entire group of 4,652 cases, yet, because of the poorer expectancy in the early age groups, this represents a fairly encouraging survival rate for the early age group.

Summary

The results of a study of the age distribution of 4,652 cases of carcinoma of the cervix have been presented, showing both the ages of incidence and the ages at admission, together with a breakdown into the age distribution of the three histologic groups.

A detailed report is given of three cases of squamous cell carcinoma of the cervix occurring in the second decade of life.

It is important that the family physician realize that malignancy of the cervix may occur at any age period after the first decade of life, and the possibility of the presence of carcinoma of the cervix should not be eliminated solely because of the age of the patient.

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THE TREATMENT OF CARCINOMA OF THE CERVIX*

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KELLY and Burnham of Baltimore in 1912 initiated the elective treatment of carcinoma of the cervix with radium. The negligible primary mortality, the absence of postoperative morbidity, the almost miraculous immediate response and the high incidence of apparent cures resulted in its adoption as the treatment of choice in most of the major gynecologic clinics throughout the world.

The technique of radiation therapy has undergone a gradual evolution during the past thirty-five years; with increase of knowledge of the physics of radiation and the biologic reaction of tissues to this form of therapy it is rare indeed to see the needless destruction of tissue which was formerly referred to as "the usual radium slough." In most clinics at the present time treatment with high voltage x-ray precedes the local application of radium. This has the fourfold advantage of devitalizing the cancer cells before local manipulation may cause their dissemination, at least partial sealing of lymphatic channels, clearing up the ever present local infection, and an amazing restoration of the cancer-distorted anatomic relationships.

At Pennsylvania Hospital we have given 2,000 to 2,800 roentgens as measured in air to one 15 by 15 centimeter port anteriorly and posteriorly. For greater protection of the bladder and lower bowel a strip of lead four centimeters wide and five millimeters thick is placed on the skin in the midline prior to each treatment. The remaining areas are filtered by one millimeter of aluminum and 0.5 millimeter of copper. Two hundred kilovolts are utilized at a distance of 50 centimeters. The effective wave length is 0.160 Au, and the half value layer is 0.90 millimeters of copper. If well tolerated, 200 roentgens are administered anteriorly and posteriorly three times each week. In our earlier cases two lateral ports were used, but this was discontinued because of the high incidence of fracture of the neck of the femur following this relatively ineffectual amount of exposure. The addition of the lead strip, which reduces the depth dose to the midline structures by 50 per cent, has diminished the number of both early and late bladder and bowel reactions.

More recently the abdominal and loin ports have been supplemented by a cervical port, the radiation being delivered through an intravaginal cone. Behney, and more recently, Taylor and Twombly, have reported promising improvements in salvage following use of this method.

Six weeks after completion of the x-ray cycle the local application of radium is made. Techniques vary widely in minor details, but the consensus is to give approximately 6,000 milligram hours to the cervical area, including the cavity of the uterus and the bases of the broad ligaments. This dosage will vary upward if small amounts of heavily filtered sources of radiation are used, or downward if larger quantities of radium are utilized. Our own technique for the past ten years at the Pennsylvania Hospital is to place three 10 milligram capsules into the cervical canal filtered by 1 millimeter of platinum. One 10

*Presented, by invitation, before the Chicago Gynecological Society, May 16, 1947.

milligram capsule filtered by 2 millimeters of platinum is placed in the vagina anteroposteriorly across the cervix, and a 10 milligram capsule similarly filtered is placed in each end of a colpostat. This technique utilizes a total of 60 milligrams of radium which is left in place for a period of one hundred hours. Not infrequently this dosage is divided into two applications at an interval of one month. Because of the potent dangers of infection and of injury to the ureters and the uterine vessels we have abandoned the use of interstitial radium needles. The lower bowel is cleansed by an enema prior to the application and a catheter remains in the bladder. The Trendelenburg position is maintained throughout the period of radiation to protect the intestinal tract.

Results of Radiation Therapy

The absolute results of any form of treatment for cancer must be based upon the number of patients who are living and free from evidence of cancer after a standard number of years compared to the number of patients who apply for treatment. The relative survival rate is calculated upon the number of patients who were actually treated. Unfortunately there is such a wide variation in methods of reporting results that comparison of survival rates is extremely difficult.

The average absolute five-year survival rate following combined radiation therapy as estimated from present-day reports is in the neighborhood of 28 per cent. It is interesting and perhaps informative to note that this rate is in direct proportion to the recognized absence of involvement of regional lymph nodes. This poses the question of whether cancerous lymph nodes are susceptible to present methods of radiation therapy.

A fair average of five-year salvage figures for growths apparently limited to the cervix is 75 per cent; for those questionably limited is 50 per cent; for those which have invaded the broad ligaments is 20 per cent; and in the group of cases in which the growth has involved the entire pelvis, the five-year salvage is practically nil.

These results, reported by a large number of surgeons and radiologists, are quite comparable with the results obtained by such master surgeons as Bonney and Wertheim with the radical operation. The primary mortality is practically nil and urinary fistulas and other untoward postoperative sequelae are rare.

Report of Cases From Pennsylvania Hospital

The following portion of this presentation is based upon the patients with carcinoma of the cervix observed and treated in the Pennsylvania Hospital from 1933 through 1941. During the first half of this period approximately one-third of the patients were treated on the general surgical service; since 1937 all such cases have been admitted to the gynecologic service where the methods of management have been more uniform.

TABLE I. CARCINOMA OF THE CERVIX, PENNSYLVANIA HOSPITAL. 1933 TO 1941

	NUMBER	PER CENT
Patients seen	130	100
Patients treated	122	94
Patients followed	125	96

As seen in Table I, only eight of the 130 patients were considered to have involvement too extensive to warrant treatment. All of these died within a few weeks of their admission. Ninety-six per cent of the patients have been

followed, despite the fact that the war years caused a considerable disruption of our cancer clinic. The five patients who were lost were counted as having died of cancer.

TABLE II. EXTENT OF DISEASE (SCHMITZ)

STAGE	NUMBER	PER CENT
I	7	5.4
II	38	29.2
III	66	50.8
IV	19	14.6
Total	130	100.0

Table II indicates that our material was composed of the usual preponderance of late cases; in two-thirds of the cases the growth had extended beyond the confines of the uterus. It is hoped and rather reasonably expected that education of the public will result in reversal of these figures.

TABLE III. AIM OF TREATMENT

	NUMBER	PER CENT
Curative	111	85.4
Palliative only	11	8.4
No treatment	8	6.2
Totals	130	100.0

The figures in Table III show that eleven patients were treated only for palliation. These were Stage IV cases in which a minimal amount of x-ray or radium therapy was utilized in the hope of temporary control of bleeding. The amount of treatment was so small in terms of curative therapy that they would be more correctly recorded as not having received any treatment. The remaining 111 cases constitute the group on which the relative survival figures are calculated.

TABLE IV. ABSOLUTE FIVE-YEAR SALVAGE

	NUMBER	PER CENT
Patients seen	130	100
Patients living 5 or more years	36	27.6

The absolute five-year salvage rate is based upon the number of survivors free from evidence of cancer as compared to the total number seen during the period. The latter figure includes nineteen patients who were not given a "curative" amount of therapy.

TABLE V. RELATIVE FIVE-YEAR SALVAGE

	NUMBER	PER CENT
Patients treated (curative)	111	100
Patients living 5 or more years	36	32.4

The relative five-year salvage is based upon the 111 patients who were given the full or near-full amount of treatment. Approximately one-third of these patients have survived from five to thirteen years with no present evidence of cancer.

The usual distribution of histologic types of growth is shown in Table VI. No attempt has been made to correlate the end-results with the histologic degree

TABLE VI. HISTOLOGIC TYPE

	NUMBER	PER CENT
Squamous cell	112	86.1
Adenocarcinoma	18	13.9
Total	130	100.0

of malignancy, as we found some years ago that the high radiation sensitivity of the more malignant tumor and the relative radiation resistance of the more slowly growing cancer account for a practical equality of end-results in the two groups. It is our belief that all patients should be given the maximal amount of radiation therapy.

TABLE VII. ABSOLUTE FIVE-YEAR SALVAGE ACCORDING TO HISTOLOGY

TYPE	NUMBER OF CASES	FIVE-YEAR SALVAGE	
		NUMBER	PER CENT
Squamous cell	112	30	23.0
Adenocarcinoma	18	6	33.3
Total	130	36	27.6

The number of cases of adenocarcinoma is too small to be significant; the results are recorded for whatever value they may be in a larger collected series.

TABLE VIII. ABSOLUTE FIVE-YEAR SALVAGE ACCORDING TO EXTENT

STAGE	NUMBER OF CASES	FIVE-YEAR SALVAGE	
		NUMBER	PER CENT
I	7	6	85.7
II	38	18	47.3
III	66	12	18.2
IV	19	0	0.
Total	130	36	27.6

Our results as shown in Table VIII confirm the accepted fact that the extent of the disease is the only valuable indicator in prognosis. Four-fifths of the Stage I cases became five-year survivors, while none of the Stage IV patients lived more than a few months.

TABLE IX. ABSOLUTE FIVE-YEAR SALVAGE ACCORDING TO "OPERABILITY"

STAGE	NUMBER OF CASES	FIVE-YEAR SALVAGE	
		NUMBER	PER CENT
I and II	45	24	53.3
III and IV	85	12	14.1
Total	130	36	27.6

These figures (Table IX) are re-arranged from the preceding table so that comparison can be easily made with survival results following radical surgical therapy. The five-year salvage of 53.3 per cent compares favorably with Wertheim's 42.9 per cent, and with Bonney's 53 per cent survival rate in 300 cases in which there was no lymph node involvement.

In Table X an attempt is made to correlate the five-year survival rate with the amount of radiation therapy. "Adequate" therapy indicates 6,000 milligram hours of radium and 2,000 roentgens of x-ray to each of four pelvic ports. "Borderline" therapy includes those patients who received from 3,600 to 6,000

milligram hours of radium and at least 1,600 roentgens of x-ray to each of four pelvic ports. The "uncoordinated" received less therapy than the "Borderline." While the number of cases is too small to warrant definite conclusions, there is an indication that our present plan of treatment offers a better chance of five-year survival than lesser amounts of therapy.

TABLE X. RELATIVE FIVE-YEAR SALVAGE ACCORDING TO ADEQUACY OF TREATMENT (STAGES I, II, AND III)

TREATMENT	CASES		FIVE-YEAR SALVAGE	
	NUMBER	PER CENT	NUMBER	PER CENT
Adequate	36	33	14	38.8
Borderline	28	25	8	25.8
Uncoordinated	47	42	14	29.8
Total	111		36	32.4

Revival of the Radical Surgical Approach

Within the past few years Meigs of Boston, Taylor of New York, Counsellor of the Mayo Clinic, Morton of San Francisco, Carter of Durham, and a few others have advocated a return to the radical Wertheim operation combined with Taussig's lymphadenectomy for the treatment of certain early selected cases. Meigs has recently detailed his reasons for this decision as follows:

"1. If the cervix is removed, there is no chance for recurrence in it.

"2. If the cervix is removed no cancer can grow in it as a recurrence.

"3. Certain cancers of the cervix are radiation-resistant.

"4. From the work of Bonney and Taussig it has been proved that about 20 per cent of patients with lymph-gland involvement can be salvaged by surgery."

Those who advocate this method restrict its use to good operative risks in whom the growth involves not more than the entire cervix and the upper portion of the vagina. It is not applicable to those in whom the parametrium is invaded.

It is a credit not only to Meigs' consummate skill, but also to the numerous advances in modern surgery that he was able to perform this exacting procedure ninety-one times without an operative death, and that he has had forty consecutive cases without development of a single urinary fistula. Of the 36 patients who had been operated upon more than three years previously, he reported in 1946 that 77.7 per cent were living and well.

Sufficient time has not elapsed for a true evaluation of this procedure. While these results are indeed excellent, they are not significantly better than those following radiation therapy in cases of similar extent. It is hoped that a few qualified clinics will continue the surgical approach until time will permit a comparison of results. In the meantime it is suggested that the rank and file of those who treat cervical cancer not abandon radiation therapy. There is little doubt that the general adoption of the radical operation would result in needless mortality and morbidity.

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Discussion

DR. HERBERT E. SCHMITZ.—At the dedication of the Tumor Clinic at Henrotin Hospital in 1939 one of the guest speakers was Dr. Joseph Vincent Meigs. During the course of his presentation he made the statement, "I believe the treatment of carcinoma of the cervix is surgical." Since that time there has been a tremendous trend mostly by those of little experience to follow in the footsteps of Meigs. I think before long he is going to realize that his end-results do not justify the heroic measures that he is undertaking with his surgical attack. It is going to take ten or fifteen years before those who have followed in his footsteps will become cognizant of that fact and finally give up radical operation. When I received Dr. Kimbrough's paper and read it some weeks ago, I thought it would be of interest to take a comparable number of years in our clinic and break down those cases to try and support what he had to say.

The one difference is this, that beginning in 1933 we instituted higher voltage x-ray in the treatment of cervical carcinoma, x-ray in the range of 800,000 volts. The radium dose that we had previously used and which had been reported in previous publications since 1914 has remained the same. Our method of radium application is to give in divided doses 4,500 milligram hours of radium placed in the cervical canal, filtered with 2 mm. of brass and 3 mm. of para rubber. The length of the capsule is altered to fit conditions predominant in the canal of the cervix.

I wish to momentarily digress from that to call your attention to a recent paper by Rusty Purtell of Seattle in which he makes the statement that the treatment of carcinoma of the cervix should be in the hands of the radiologist, and that the results will never be satisfactory if the gynecologist is going to carry on radium treatment, and the radiologist roentgen ray therapy. He says it takes the knowledge of the radiologist in physics of radiation to know how to apply radium because of the changes in the cervical canal. It is my opinion that the gynecologist is more competent to dilate the cervical canal and apply radium than the radiologist. I think we should rise in defense of our position there.

During a comparable period, 1933 to 1942, there were 422 cases of carcinoma of the cervix in the Institute. I have broken this down into recurrent and primary cases, because with the advent of higher voltage many patients were sent in to the Institute who had previously been radiated in the hope that the higher voltage would be of benefit. We know very definitely that previous radiation alters the sensitivity of the cancer cells to radiation, not only because of the effect on the cell itself, but because of a change in the environment in which that cell finds itself; in other words, the sensitivity of the tumor cell in the cervix is altered when it goes into the vagina or vaginal mucosa. Therefore, we must delete these recurrent cases. That leaves us with 166 cases during that time that had no previous radiation. Dividing those into the four groups of Schmitz we have:

Group I	11 cases
Group II	37 cases
Group III	70 cases
Group IV	48 cases

It is interesting to note the slight variation in Groups I and II, Dr. Kimbrough having seven in Group I and thirty-eight in Group II. In Group III the radiation as carried out is 800 kilovolts x-ray with a filtration of 1 mm. of lead, 1½ mm. of tin, 2 mm. copper, and 3 mm. aluminum. Our aim is to give 4,000 r into the midpelvis and into the tumor-bearing area. If we can do that with two fields we do not resort to three or four. We have been told if you use a large field of x-ray at the outer limits of your field you lose so many roentgens. With 10 cm. depth dose we lose four to ten roentgens at the outer edge; with

a 20 by 20 cm. we only lose one roentgen, so that with that slight difference we prefer to use a large field where we can get homogeneous radiation into the pelvis. If we apply this was 4,500 radium hours we are getting a dose somewhere in the neighborhood of seven erythema doses. If we accept the evidence of Wood, Prime, or Quimby that it takes ten erythema doses to produce resistance, we can understand why some cases respond and some do not and why the end-results are definitely proportional to the extent of the disease.

Our experience with adenocarcinoma runs in the neighborhood of two and one-half per cent. That is lower than the average.

The comparison of the five-year salvage shows that in Groups I and II the end-results are certainly as favorable as anything that has been offered to us by surgical attack. The mortality was nil. I could not agree with Dr. Meigs that we have very definite evidence that the treatment of carcinoma of the cervix is radical. Whether or not if we were to do a postradiation hysterectomy some of these people who had a recurrence five years after would have been saved, I am not in position to answer. If we look at the work of Lynch and if we follow the work of Morton I think eventually we will have the answer to that.

DR. EUGENE A. EDWARDS.—I agree with the opinions expressed by the essayist most completely. Certain statements are worthy of emphasis:

All patients with carcinoma of the cervix should be completely and adequately radiated.

The percentage of five and ten-year cures depends upon the extent of the lesion, rather than the microscopic characteristics of the tumor tissues. Therefore the percentage of cures will be the direct result of the establishment of the diagnosis of early localized carcinoma. The early diagnoses of cancer of the cervix are made in patients who are examined routinely and by a routine biopsy of all suspicious lesions.

Education of the public has aided in a higher percentage of cures.

X-ray therapy may or may not kill cancer cells in distant pelvic lymphatics.

The surgical treatment of carcinoma of the cervix, as the essayist has indicated, is receiving increased attention, and several groups are treating selected cases in this manner. Such management by a few well-chosen groups is justified in the light of the more recent advancements in surgical techniques, and pre- and postoperative management, such as chemotherapy and blood transfusions.

The procedure should be done only by those groups who have a large number of such patients and that can follow these patients and can present to us their results.

The management of the hopeless cancer still remains a difficult problem. It is our opinion that the cancer patient who has received adequate treatment and has recurrences is entirely a medical problem, and not a surgical one. We believe that too many of these people have unnecessary surgical operations. Palliation is the treatment of choice. Morphinism should be prevented.

Dr. Kimbrough advocates waiting six weeks after the completion of the x-ray therapy before applying radium. We have not considered such a period of time as necessary, and, in fact, have believed the sooner the radium was applied, the better. I would like to ask the reason for the delay.

DR. KIMBROUGH (Closing).—The reason for the delay of six weeks in giving radium treatment following the completion of the x-ray cycle is an attempt to avoid untoward reactions in the bladder and lower bowel. We were having so much difficulty with immediate proctitis and late rectal strictures, and so many atrophic ulcers of the bladder that we decided to adopt this interval. We believe we have lowered the incidence of these sequelae.

CHANCRE AND CARCINOMA OF CERVIX, SIMULTANEOUS OCCURRENCE ON OPPOSITE LIPS

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CHANCRES of the cervix undoubtedly occur more frequently than the literature would have us believe. The recognition and diagnosis of such lesions, however, is certainly uncommon when compared with the frequency of primary lesions of the external genitals. The simultaneous occurrence of both chancre and carcinoma on separate cervical lips is unquestionably a rarity. In a fairly extensive review of the literature and upon questioning numerous gynecologists and syphilologists, we have been unable to find a parallel case. Because of this apparent rarity as well as to emphasize the importance of an accurate etiological diagnosis of cervical erosions and ulcerations, the following case is reported.

Case Report

Mrs. C. O., aged 48 years, was first seen (E.P.S.) on Aug. 22, 1946, with a chief complaint of vaginal bleeding. This had persisted since the onset of an apparently normal period which began July 27, 1946. Essential aspects of the history were as follows: menses began at the age of 14 years and were of the 28 to 30 day type with a seven-day flow. The patient denied syphilis and gonorrhea by name and symptomatology, although several suspicious sexual exposures had occurred within the past two months. Previous serologic tests for syphilis were negative. The patient had had two pregnancies, both of which had terminated normally—one sixteen and the other fourteen years ago.

Physical examination revealed an obese individual appearing of about the stated age, and in apparent good health. A complete physical examination was essentially normal with the exception of the pelvis. Pelvic examination revealed normal distribution of pubic hair and entirely normal external genitals. There was no evidence of cutaneous or mucosal lesions about the external genitals. The perineum was relaxed. A small asymptomatic cystocele was noted, and the cervix felt large and soft to the palpating fingers. The uterus was normal in size, shape, position, and consistency, and was freely movable. No abnormal masses were felt in the adnexa, and no parametrial induration or fixation was felt. There was moderate bleeding following digital examination.

Inspection of the cervix revealed an ulcer, 1 cm. in diameter, on the anterior lip covered with a grayish membrane. Following mechanical cleansing slight bleeding was observed from this ulcerated area. The edges of the ulcer presented no more induration than the cervix elsewhere. The anterior lip exclusive of the ulcer was pale and edematous. The posterior lip revealed a hypertrophic and slightly fungating ulceration from which slight bleeding was observed.

From the appearance of the lesion on the posterior lip, a tentative diagnosis of carcinoma was entertained. It was felt that the ulceration of the anterior lip was a separate entity and, although a definite diagnosis was not made, the resemblance to primary syphilis was noted, and such a diagnosis was given serious consideration. A serologic test for syphilis was made at this time but no dark-field examinations were done.

On Aug. 26, 1946, biopsies were taken from both lesions. Because of technical difficulties at the time, frozen sections, as requested, were not done. Serologic tests were repeated. Two days later, positive Kahn tests were reported from two different laboratories, and the patient was then sent for the first time to a syphilographer (A.B.L.) for examination and dark-field examination. This examination revealed numerous treponema pallida from the ulcer on the anterior lip. No other type of spirochetes were observed. Further serologic tests were made at this time which included Kahn and Kline tests. Both were strongly positive.

Antisyphilitic therapy was commenced immediately. On Aug. 31, 1946, the pathologic report revealed a squamous cell carcinoma of the posterior lip and syphilis of the anterior lip. There was no concomitant evidence of syphilis in the material taken from the posterior lip. A complete pathologic report furnished us by Dr. Harold Gordon follows:

"*Microscopy:* The sections consist of several biopsies of the cervix uteri showing two unrelated lesions.

"Some of the fragments are almost completely replaced by granulation tissue, only a few cervical glands and a small portion of mucous membrane being visible. There is extensive ulceration of the surface. The base and margins of the ulcer consist of vascular granulation tissue with swelling and proliferation of the vascular endothelium; with severe arteritis of some of the older vessels; with confluent perivascular mantling of monocytes, fibroblasts, lymphocytes, and plasma cells; and with diffuse inflammation extending into the periphery. These changes are quite characteristic of a primary chancre.

"Other portions of the cervix show invasion of some of the glands and adjacent tissue by squamous cell carcinoma. The carcinoma cells are hyperchromatic and vary in size, but are comparatively well differentiated. There is fibrosis about some of the cancer cell nests and the blood vessels are thick walled, suggesting that the cancer probably was preceded by prolonged irritation and low-grade chronic inflammation.

"*Diagnosis:* Squamous cell carcinoma of cervix (Grade II). Primary chancre of cervix."

The patient was hospitalized on Sept. 5, 1946, for continuation of her treatment for syphilis and radium therapy. On Sept. 6, 1946, she was given 5,000 milligram hours of radium. Total antisyphilitic therapy consisted of 6,000,000 units of penicillin (60,000 units every three hours) 240 mg. of Mapharsen, and 0.39 Gm. of bismuth subsalicylate. Subsequently, the patient received 20 deep x-ray exposures to the four pelvic portals and intravaginally for a total of 6000r units. On Feb. 7, 1947, a cerebrospinal fluid examination was done which was negative throughout. This included a Wassermann, colloidal gold, globulin, total protein, and cell count. The patient's condition gradually improved and her serologic tests gradually became negative and have remained so. Two postirradiation biopsies were done, the last on Sept. 25, 1947, and neither showed any evidence of residual malignancy.

Historical

Gellhorn and Ehrenfest[1] stated that Gosselin in 1843 is reputed to have first called attention to the fact that ulcerations of the cervix may result from syphilis. A year later Bennet described the typical Hunterian chancre of the vaginal portion of the cervix. The recognition of the cervical chancre as a definite pathologic lesion, however, dates from the excellent observations of Fournier in his *Leçons* written in 1873. Gellhorn[2] found many reports of chancres of the cervix prior to 1905. In that year, however, Schaudinn's discovery of the spirocheta pallida demanded greater accuracy in diagnosis, and thereafter fewer reports appeared. Although dermatologists have contributed largely to our knowledge of syphilis, it is gratifying in passing to mention that Paschen, a gynecologist, was the first to confirm Schaudinn's discovery by demonstrating treponema pallida in a cervical chancre.

Discussion

Most series presented in the literature of chancre of the cervix comprise comparatively few cases, and the incidence has been variously estimated from 1 to 10 per cent of all cases of syphilis in women. This seemingly low incidence is almost undoubtedly an underestimate, for syphilologists and gynecologists alike readily admit that in many cases of frank secondary syphilis in women the primary lesion is overlooked. It is difficult to conceive of so many cases of secondary syphilis without the patient having primary lesions at some time. Excluding the external genitals and extragenital chancres (about 10 per cent) the most likely location of such a lesion is the cervix. According to Wile,[3] such lesions should be very common, since the chancre in men is most frequently situated at or near the distal portion of the male organ, and infection usually occurs during coitus.

Fig. 1.

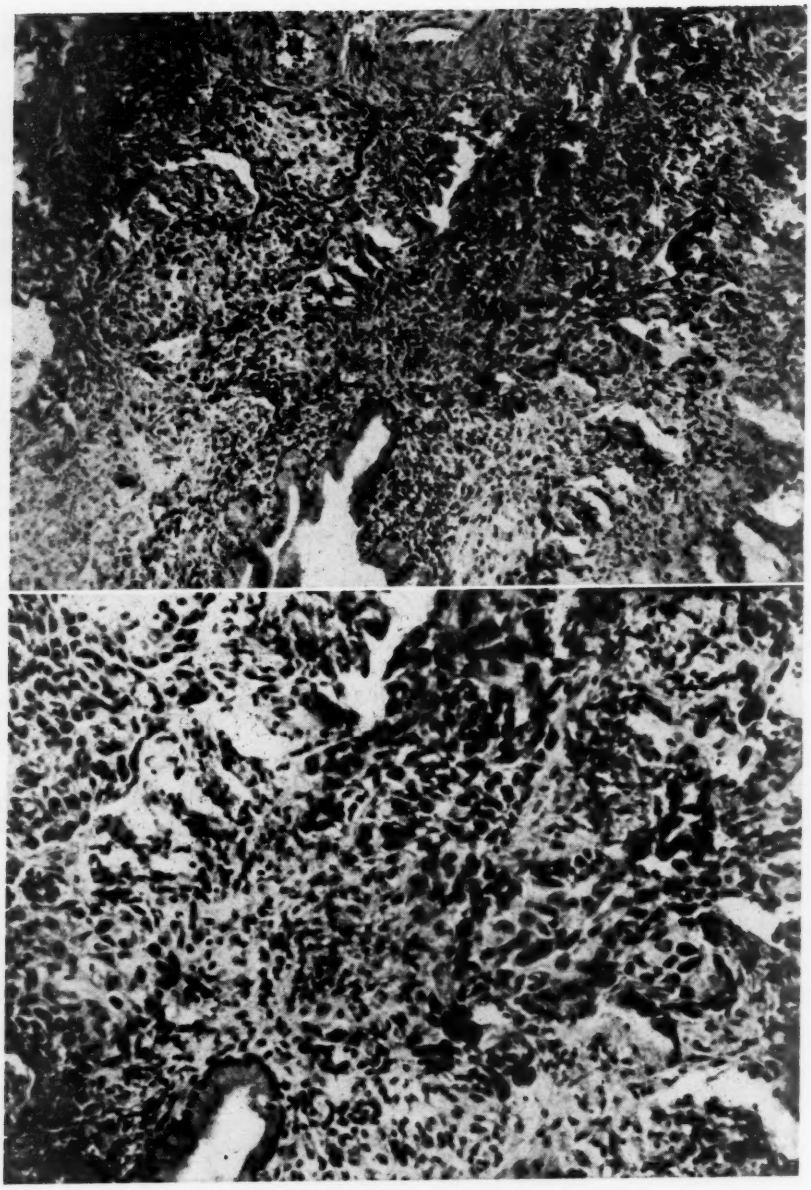

Fig. 2.

Fig. 1.—Photomicrograph of tissue taken at biopsy from posterior lip of cervix showing Grade II squamous cell carcinoma. ×100.

Fig. 2.—Higher power of section of the carcinoma. ×400.

Fig. 3.

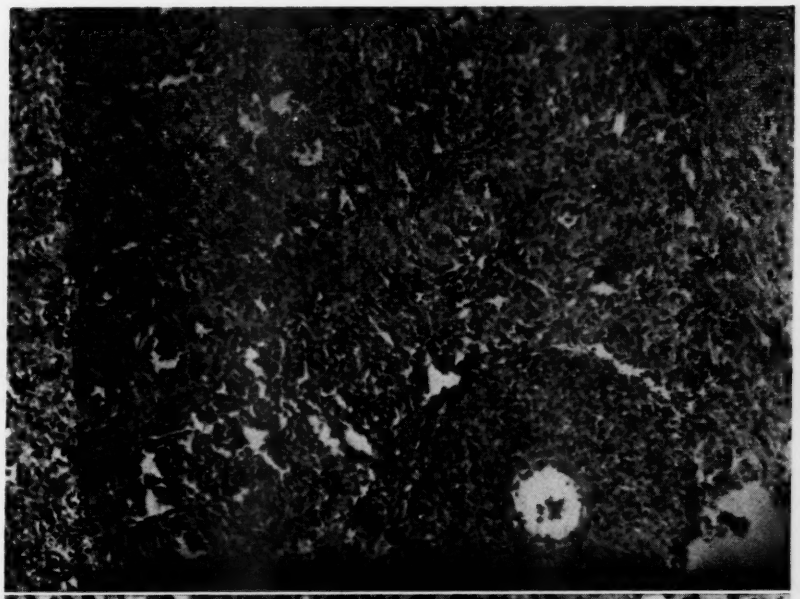

Fig. 4.

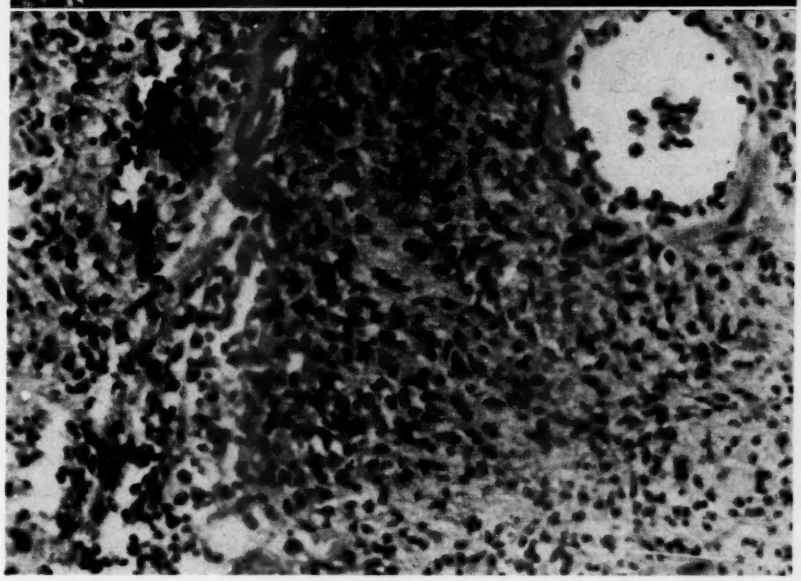

Fig. 3.—Photomicrograph of tissue taken at biopsy from ulcer on anterior lip showing chancre. ×100.

Fig. 4.—Higher power of section of chancre. ×400.

The exact anatomic location of chancre of the cervix has been variously described. Guerriero,[4] in reporting twenty-seven cases, found the lesion surrounding the external os in 55 per cent. The anterior lip alone was involved in 30 per cent, and the posterior alone in 15 per cent. Stookey[5] expressed the opinion that the lesion tends to be disposed away from the external os, whereas others have found the anterior lip alone predominantly involved. Thus every portion of the cervix must be looked upon suspiciously for harboring such a lesion.

Judging from cases reported in the literature, the clinical appearances of chancres of the cervix differ so greatly that no distinctive features can be taken as affording a positive naked eye diagnosis. In size, they have been described as varying from a small flat erosion to a large hypertrophic, fungaceous mass nearly filling the vagina. In appearance, there may be the small erosion, a deep ulceration, a diphtheritic ulcer, or the vegetative mass highly suggestive of malignancy. In all of these various types there most often occurs the so-called "cold edema" of the cervix, produced by an outpouring of lymphocytes into lymphatic spaces with little if any extravasation of serum. Stookey,[6] in studying primary syphilitic lesions, has been particularly impressed with this edema and has stated that such edema, with or without ulcerations, may be the sole clinical manifestations of chancre of the cervix. This is especially true when a previously healthy cervix is infected. These cervices appear swollen, pale pink, soft, and doughy in consistency. The induration, which is a classic feature of chancres elsewhere, is of little or no value in the cervix, as this organ is normally firm to the examining finger.

Simple erosion and carcinoma cannot be positively differentiated from chancre of the cervix except by dark-field examination and/or examination of tissue. In a noteworthy and exhaustive study by Gellhorn and Ehrenfest in 1916, they regarded such differentiation as by far the most important problem connected with syphilis of the female genitals, and this belief must be maintained. A. S. Warthin[7] stressed the similarity of carcinoma and chancre of the cervix, and contended that it was impossible to make the differentiation by gross examination. Over a six-year period, eight cases of chancre of the cervix were sent to the University of Michigan Laboratory that were not suspected clinically. One was a uterus removed for supposed carcinoma, four were cervices amputated, and the remaining three were biopsies for suspected malignancy. In all cases, the correct diagnosis could have been established by dark-field examination and surgery avoided. To appreciate the gross similarity of chancre of the cervix and carcinoma, it is of interest to quote in part Dr. Warthin's description of one of the cases of chancre: "it (the cervix) was enlarged, indurated, irregularly nodular or cauliflower-like, its surface showing shallow ulceration covered with a thin grayish membrane about the size of a silver dollar, completely encircling the external os, but more nodular on the anterior lip. It involved the entire vaginal portion. The consistency was very hard without crumbling—."

It has been known for some time that syphilis is not infrequently a precursor of carcinoma, i.e., carcinoma may develop upon a previous syphilitic glossitis, and cutaneous gummata have likewise been the original seat of subsequent carcinomatous transformation. In the case herewith reported, no such thing occurred, however, for the original lesion in the first place was a chancre, and then again was anatomically separated from the carcinoma by apparently normal cervical tissue. It is further recognized that any open ulcerative area is fertile soil upon which a chancre may develop, but this was likewise not true. The lesions in the cervix in this case were not only clinically distinct and separate entities, but there was likewise no histologic evidence of chronic infectious granuloma in the malignant area. The possibility of autoinoculability of chancre superimposed upon the carcinoma was likewise similarly excluded by the above.

Diagnosis

A high index of suspicion by both gynecologists and obstetricians is the prime requisite for the diagnosis of chancre of the cervix. Such a diagnosis, although a clinical suspicion, is confirmed only by a positive dark-field examination for the treponema pallida. Regional adenopathy is rarely of aid in diagnosis, and the so-called satellite bubo, so characteristic of

chancres elsewhere, is seldom if ever seen in cases of chancre of the cervix. The reason for this is the fact that cervical lymph drainage is to the deep iliac, hypogastric, and pararectal glands, although occasionally some minimal inguinal adenopathy may result from anastomosis of these and parametrial glands. Pain, either spontaneous or to touch is not present, and the lesion frequently causes no disturbance of any sort. Leucorrheal discharge is dependent upon the size of the lesion and varies in amount from slight to considerable, and is usually seropurulent in character. Contact bleeding may be a symptom.

Summary and Conclusions

1. A case of chancre and carcinoma occurring simultaneously and upon opposite lips of the cervix is reported. To our knowledge no parallel case has been reported in the literature.

2. The diagnosis of chancre of the cervix is a laboratory diagnosis, but the recognition of such cases depend upon a high index of suspicion and the more frequent use of the dark-field microscope.

3. Dark-field examinations of the cervix should be performed upon all women with secondary syphilis upon whom no primaries can be demonstrated. Likewise, all cervical erosions or ulcerations whose etiology is not apparent in sexually active females should have a dark-field examination for syphilis.

4. Syphilis of the cervix if not treated may cause a partial stenosis of this organ leading to cervical dystocia in labor.

We wish to thank Dr. J. R. Blumenthal for the original pathology report and Dr. Harold Gordon for a subsequent report and for preparation of the photomicrographs.

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Note.—Since submission of this report, the patient has been seen regularly. On May 13, 1948, cervical biopsies were negative and no clinical or laboratory evidences of residual malignancy or syphilis were demonstrable.

CHANGING TRENDS IN CESAREAN SECTION*

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A STATISTICAL study of cesarean section at Morrisania City Hospital from 1929 to 1937[1] and a related analysis of unengaged vertex presentations in full-term primiparas[2] revealed that the maternal and fetal mortality could be reduced by broadening the indications for cesarean section without increasing the incidence for this operation to abnormal levels. When these papers were published, the cesarean incidence was 0.8 per cent, one of the very lowest in New York City.

Since that time, ten years have passed. The staff is more experienced and better able to evaluate the cases. The x-ray has come to be of great assistance in helping to differentiate types of fetopelvic disproportion. Antibiotics are available in adequate amounts. Blood transfusions are administered freely, with less danger of reactions. All these factors must influence the mortality and morbidity rates. Accordingly, another study of cesarean section was undertaken, covering the years 1938 to 1945, inclusive, to determine if the expected improvement had been accomplished.

The total number of deliveries during this latter period is much less than in the first report (Table I), but the number of cesarean operations has increased from 112 to 127, making an incidence of 1.5 per cent. This incidence is almost double that of the first report. The increased cesarean incidence is compensated for by a reduction in the maternal death rate from 10.7 per cent to 3.3 per cent. It is interesting to note that the over-all maternal deah rate has also dropped from 5.3 per thousand terminated pregnancies to 2.3, indicating a general improvement for the entire service. As will be seen, the better results with cesarean section undoubtedly played a large part in accomplishing this improvement.

TABLE I

	1929-1937	1938-1945
Total deliveries	14489	8356
Maternal deaths per 1000 terminated pregnancies	5.3	2.3
No. of cesarean sections	112	127
Incidence of cesarean section	0.8 per cent	1.5 per cent
No. of maternal deaths	12	4
Maternal mortality rate, cesarean section	10.7 per cent	3.3 per cent

The indications for cesarean section are listed in Table II. For the purposes of discussion each indication will be treated separately, with the exception of the minor indications. In this way, it is to be hoped that the major changes which have taken place will be clearly brought out.

*Presented at a meeting of the Bronx Obstetrical and Gynecological Society, March 22, 1948.

TABLE II. INDICATIONS FOR CESAREAN SECTIONS

	1929-1937		1938-1945	
	CASES	MATERNAL DEATHS	CASES	MATERNAL DEATHS
Cephalopelvic disproportion	47	6	44	0
Previous cesarean section	19	1	35**	0
Placenta previa	19	2	34	3
Premature separation placenta	10	2	7	1
Obstructing tumor	6	0	2**	0
Toxemia of pregnancy	1	1	3	0
Cardiac disease	4	0	–	–
Other indications:	7	0	4	0
Ruptured uterus	2*	0	–	–
Previous attempted delivery	1	0	–	–
Vaginal stenosis	1	0	–	–
Cervical stenosis	3	0	–	–
Previous stillbirths	–	–	2	0
Condyloma acuminata	–	–	1	0
Transverse presentation	–	–	1	0
Totals	112	12	127	4

*1 case included in group of previous cesarean section.
**1 case included in group of placenta previa.

Cephalopelvic Disproportion

More than one-third of all the cesarean sections were done because of this indication. It will always be so, because cephalopelvic disproportion is one of the most troublesome problems that confronts the obstetrician.

At least 10 per cent of all primiparas are admitted with an unengaged presenting part, and while 90 per cent of these cases will eventually deliver vaginally, it takes keen judgment to determine which will do so with least injury to the mother and her baby. The incidence of cesarean section in this group can be very high, indeed, if one adopts a strict attitude of operating on any such case if the membranes have been ruptured six hours or the head is not engaged within six to twelve hours of active labor. Such criteria will increase the cesarean incidence to 4 per cent or more and the maternal mortality emanating from such centers will of course be very low because of the excellent conditions under which such patients are operated upon. We are not in accord with this policy.

TABLE III. TYPES OF CEPHALOPELVIC DISPROPORTION

	NUMBER CASES	MATERNAL MORTALITY	NUMBER CASES	MATERNAL MORTALITY
Cephalopelvic disproportion	47	6 (12.9%)	44	0
Absolute disproportion	11	0	18	0
Relative disproportion	36	6	26	0
Elective cesarean sections	13	3*	17	0

*2 died of peritonitis, 1 died of postoperative pneumonia.

Cephalopelvic disproportion should be recognized immediately on admission to the hospital. In a ward service such as ours, the problem first confronts the intern staff, who are least experienced in obstetrics. The subject of unengagement, therefore, is constantly stressed at daily rounds in order to keep the intern alerted to this physical sign. He in turn notifies the resident, and, if the diagnosis is verified, an immediate x-ray pelvimetry is done and a member of the Attending Staff called. Cases of absolute disproportion are immediately operated upon, unless a fetal anomaly is known to exist. Those patients with

an ample pelvis and average-to-small babies, who really have no disproportion and in whom the presenting part can be Müllerized into the pelvis, are permitted to labor as would any patient with an engaged head.

Patients who do not fall into either of the above categories are cases of relative disproportion. Most of them will also deliver per vaginam but it is often difficult to choose the ones who will do so, without ending in a difficult forceps delivery and a badly mauled mother and baby. It has been our experience that the fetal mortality rises as high as 41.6 per cent if these cases are not delivered within forty-eight hours of labor.

Unless contraindications for a test of labor exist, such as symptomatic heart disease, tuberculosis, toxemia of pregnancy, elderly primipara, patients with relative disproportion were given a test of labor which was not to exceed twenty-four hours. If the membranes were ruptured that length of time and progressive labor had not set in, a cesarean section was done. If the cervix reached four-finger dilatation within the twenty-four hour period and the head was not engaged shortly thereafter, a cesarean section was done at that point and not at the end of twenty-four hours. Failure of the cervix to dilate steadily in that time was also grounds for doing a cesarean section.

The facts indicate that we have made no radical departure from our original attitude toward cephalopelvic disproportion. This is best judged by the number of elective cesarean sections. There were only 17 elective sections in the last study as compared to 13 in the first report.

The most striking statistical finding is the drop in maternal mortality from 12.9 per cent to zero in this group. We attribute this improvement to the type of operation and to the use of antibiotics, all of which will be discussed later.

The only stillbirth in this last series occurred when the routine, as outlined above, was not adhered to. The patient was a primipara at full term, admitted with a history of ruptured membranes for thirty-two hours and irregular pains. The cervix was 1½-fingerbreadths dilated and thick. After twenty-four hours' observation, the question of disproportion arose. X-ray pelvimetry was then done, which disclosed a true conjugate of 9.5 cm. and the presenting vertex unengaged. A low-flap cesarean section was performed. The amniotic cavity was infected. The baby was delivered in poor condition and died a few minutes later. The patient ran a stormy course, complicated by a disruption of the abdominal wound that was successfully repaired, and a pelvic abscess which was drained through the vagina. Eventually she made a complete recovery. This case occurred before the use of antibiotics.

Previous Cesarean Section

The number of cesarean sections in this group has practically doubled, which is to be expected as the hospital grows older. Every precaution was taken to operate upon these women under the best possible conditions. 30 of the 35 cases were elective cesarean sections. The remaining 5 cases were in labor from six to twelve hours and one had ruptured membranes for over twenty-four hours before admission. There was no maternal mortality.

Three babies were lost: one at the time of operation, one seven hours postoperatively, and the third died twenty hours after birth. This fetal mortality emphasizes the need for caution in guaranteeing a live baby by means of cesarean section.

Placenta Previa

The number of cesarean sections for placenta previa have almost doubled. This has been due to the inclusion of more cases of partial placenta previa and an occasional case of marginal placenta previa.

During the years covered by the first report, it was our policy to treat all cases of central placenta previa by cesarean section. Our attitude is still the same.

TABLE IV

	1929-1937	1938-1945
Placenta previa	19	34
Maternal deaths	2 (10.5 per cent)	3 (8.8 per cent)
Central placenta previa	15	10
Partial placenta previa	4	16
Marginal placenta previa	0	8
Stillbirths	1 (premature)	3 (1 premature)
Neonatal deaths	5 (premature)	5 (3 premature)

The other varieties of placenta previa, however, were delivered vaginally, except for an occasional case of partial placenta previa that was bleeding too actively on admission. The fetal mortality, even after correction for prematurity, and the maternal morbidity were much too high and brought about the adoption of the following attitude; namely, that every proved case of placenta previa is to be treated by cesarean section unless the vaginal examination reveals that delivery per vaginam can be accomplished without too much risk to the mother and baby. The occurrence of active bleeding and a thick, incompletely dilated cervix in a primipara were considered sufficient cause for cesarean section, no matter what the type of placenta previa and the state of viability of the baby. Multiparas with soft, partly dilated cervix and intact membranes were treated in a manner very similar to mild instances of premature separation of the placenta; i.e., by rupture of the membranes and administration intramuscularly of small amounts of pituitrin. In fact, we look upon symptomatic placenta previa as merely a premature separation of an abnormally situated placenta.

The maternal mortality is still high (8.8 per cent as compared to 10.5 per cent in the earlier study). Two deaths were due to peritonitis at a time when antibiotics were still not available for civilian use. The third death resulted from hemorrhage, the patient being practically exsanguinated on admission.

Premature Separation of Placenta

In the first study we stated that "the Dublin method (of treatment for premature separation of placenta) should be used only where blood transfusions can be readily obtained and where trained personnel is available. Lacking such facilities, the interest of the patient is best served by a cesarean section." This policy has been carried through into the second study.

TABLE V

	1929-1937	1938-1945
Premature separation placenta	10	7
Partial	3	4
Complete	7	3
Maternal deaths	2	1
Stillbirths	7	3
Neonatal deaths	2	1

There was one maternal death whose case history is given briefly in order to bring out an important lesson. A primipara, aged 36 years, was referred to the hospital at term with severe pre-eclamptic toxemia and a complete ablation of the placenta. An immediate cesarean section was done, a stillbirth delivered, the uterus was packed, 5 Gm. of sulfanilamide were instilled into the peritoneal cavity, and the patient transfused with 2,000 c.c. of blood. She went into uremia and died in 4 days. In discussion of this case at one of our conferences, it

was brought out that the sulfonamide may have contributed to the additional renal damage and turned the table against her recovery.

Obstructing Tumors

With the exception of cervical fibroids, tumors obstructing the pelvis offer no surgical dilemma as to the method of therapy, except for the technical difficulties which may be encountered. Cervical fibroids may become very troublesome by preventing adequate lochial drainage, especially if the fibroid is located on the posterior cervical wall. Blockage of the lochia may lead to a breakdown of the uterine incision and consequent peritonitis. The two cases in the last series were treated by cesarean hysterectomy to avoid any such complication. One fibroid bulged forward so far as to prevent closure of the incision in the anterior wall of the lower uterine segment.

Toxemia of Pregnancy

We have routinely treated eclampsism and hypertensive toxemia of pregnancy according to a modified Stroganoff regime, followed by induction of labor. In the first study, a severely convulsive primipara, who failed to respond to this treatment, was sectioned but died in coma in twenty-four hours. The baby was born dead.

Three cases of toxemia were sectioned in the current group. One was a para vi, gravida vii, aged 38 years, with a long-standing hypertension. A cesarean section was done because a sterilization of the tubes was necessary. The second case was that of a pre-eclamptic, at term, not in labor, also a multipara who required tubal sterilization. The third case was a primipara, aged 13½ years, who was admitted in severe pre-eclampsia and went into convulsions while receiving the Stroganoff regime. She was watched for four days without improvement. A Watson induction was unsuccessful. She was delivered by cesarean section of a living baby and then recovered.

The vast majority of our toxemia cases are still being treated conservatively. Toxemia in this community is mainly a disease of the poorer classes. The admissions to Morrisania City Hospital are mainly from this group and it is not unusual for two or three such cases to be under observaton in our antepartum room at all times. Three cesarean sections in eight years (2 of which were done, not because of the toxemia, but because of the tubal sterilization) are a small percentage indeed. All of our toxemias are now under study to determine whether the end results justify a continuance of our conservative policy.

Cardiac Disease

Four cardiac patients were treated by cesarean section in our first report, three of which sections were for the purpose of doing a sterilization operation. There were no cardiac patients sectioned in this second report because the tubal sterilization operation is performed during the postpartum period, as advocated by Fred L. Adair and Ira Brown.[3]

It is our opinion that cesarean section should not be done for cardiac disease per se, provided conditions prognosticate a normal delivery. On the other hand, no cardiac patient should be given a trial of labor in the presence of a possible disproportion.

Other Indications for Cesarean Section

These consisted of two instances in which the patients had had previous stillbirths resulting from difficult labors due to borderline pelves: one patient

with an extensive condyloma acuminatum involving the vulva and the vagina, in whom it was desired to avoid injury to the extensively infected soft parts, and one case of transverse presentation due to a marked hypertrophy of the anterior wall following a ventrofixation that caused an obstruction in the lower uterine segment.

There were no deaths in this group.

Type of Operation

The type of operation most commonly performed in this last series is the low-flap cesarean section. We were convinced by the first study that the low-flap operation gave the patient three times as much security against peritonitis as the classical section. It is still true.

TABLE VI. INDICATIONS AND TYPE OF CESAREAN SECTION

INDICATIONS	TYPE CESAREAN SECTION			
	CLASSICAL	LOW FLAP	WATERS	PORRO
Cephalopelvic disproportion	2	40	2	0
Previous cesarean section	8	27	0	0
Placenta previa	16 (1 died)	17 (2 died)	0	1
Premature separation of placenta	4 (1 died)	3	0	0
All other indications	2	4	0	1
Totals	32	91	2	2
Maternal deaths	2	2	0	0
Cause of death				
Peritonitis	1*	1*		
Hemorrhage		1*		
Uremia	1**			

*Placenta previa.
**Premature separation placenta.

Most of the classical cesarean sections were done for placenta previa or premature separation of the placenta because opinion is divided as to which operation is preferable. The senior author dislikes invading the placental bed, which gives added maternal bleeding and fetal anoxia.

The Waters' extraperitoneal operation was attempted three times, twice successfully. The third case was discontinued when the bladder was accidentally opened. The bladder was repaired and a low-flap cesarean section done. The patient recovered with only mild morbidity.

The two Porro cesarean sections were for placenta previa complicated by large fibroid in lower uterine segment, and a case of transverse presentation that could not be delivered by internal version because of a tremendously hypertrophied anterior uterine wall resulting from previous ventrofixation.

Effect of Antibiotics

Prior to the use of antibiotics, there were two deaths from peritonitis. Since sulfanilamide and penicillin have been added to our armamentarium, there have been no deaths from peritonitis. It is our impression that these drugs have further increased the safety of cesarean section. The wound infections, seventeen (24.5 per cent) in 70 cases, not treated with antibiotics compared to 7 wound infections (12 per cent) in 58 cases treated by antibiotics.

All of the cases treated with sulfanilamide had 5 Gm. of the drug instilled into the peritoneal cavity, care being taken to avoid getting any of the powder in the abdominal wall. Within twenty-four hours, the blood concentration of

TABLE VII. EFFECT OF ANTIBIOTICS ON CESAREAN MORTALITY

	NO ANTIBIOTICS		ANTIBIOTICS {SULFONAMIDES, 48 CASES; PENICILLIN, 2 CASES; S AND P, 7 CASES}	
	CASES	MATERNAL DEATH	CASES	MATERNAL DEATH
Classical	13	1 (Peritonitis)	19	1 (Uremia)
Low flap	54	2 (1 Peritonitis) (1 Hemorrhage)	37	0
Waters	2	0	–	–
Porro	1	0	1	0
Totals	70	3	57	1

sulfonamide was adequate and was maintained for three days, after which, if any further sulfonamide therapy was needed, it was given orally or intravenously. A few of these patients have had a repeat cesarean section and, in some instances, there were thick and extensive adhesions of the lower portion of the uterus to the anterior abdominal wall. This adhesive reaction was far more extensive than that attributable to a local peritonitis. Others have described the same findings and, for that reason, we are inclined to feel that in these particular cases the adhesions are related to the introduction of the sulfanilamide intraperitoneally.

Earlier in the text, a case was described in which a cesarean was done for complete separation of the placenta in a severe pre-eclamptic. This patient received a sulfonamide intraperitoneally and subsequently went into coma. It is felt that the sulfonamide may have added to the patient's difficulties through additional renal damage. We had another case in which the patient was sulfasensitive and almost died because of an allergic reaction.

These experiences with sulfonamides have influenced us away from the further use of them, more particularly since the advent of penicillin. In this report, only two patients received penicillin alone. However, we have continued to use penicillin intramuscularly as a routine ever since, with equally good results as with sulfonamides and without the sulfonamide reactions.

Summary and Conclusions

A review of the cesarean sections at Morrisania City Hospital from 1938 to 1945 reveals a reduction of maternal mortality to 3.3 per cent as compared to 10.7 per cent in a previous review.

The incidence of cesarean section has increased to 1.3 per cent as compared to 0.8 previously. The increased number of cesarean sections occurred mainly in the groups of cephalopelvic disproportion and placenta previa.

The reduction in maternal mortality is attributed to the predominant use of the low-flap operation, the routine use of antibiotics, improved technique of operation, and an attempt to prevent procrastination by properly evaluating labor at the time of admission. It is believed that a continuation of this policy will bring about a further reduction in the maternal mortality rate without adding to the incidence of cesarean section.

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THE ROOMING-IN PLAN FOR MOTHERS AND INFANTS*

An Appraisal From the Obstetric Viewpoint of One Year's Experience at the Grace-New Haven Community Hospital (University Service)

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ROOMING-IN is a term applied to that form of hospitalization in which the mother and newborn infant room together and the mother takes as much care of the baby as possible.[1] For purposes of study and evaluation, this plan has been carried out since Oct. 29, 1946, at the Grace-New Haven Community Hospital in a four-bed unit adapted for the purpose.

The development of the plan was a cooperative effort shared by the Departments of Pediatrics and Obstetrics and Gynecology of the Yale School of Medicine, the Yale School of Nursing, and the Grace-New Haven Community Hospital. The work of the unit is under the supervision of a committee representing these divisions.†

It may be useful to consider some of the thinking which led to the study of this plan of hospitalization. It is not a new procedure, for in certain European countries it still exists in many modern hospitals. In this country, however, this obviously natural arrangement was abandoned in favor of the hospital nursery system, which was developed to improve the standards of infant health. This improvement has been realized to a great degree. Nevertheless, it is the belief of many that the present system of separation of the infant from its mother may interfere with certain essential needs of both mother and child and that the present rigid infant-feeding schedule is a considerable factor in the background of so-called problem children.

An important contribution to the subject was made by Simsarian and McLendon,[2] in 1942, in a report on "The Feeding Behavior of an Infant During the First Twelve Weeks of Life on a Self-Demand Schedule." In 1945, McLendon and Parks[3] published "Nurseries Designed for Modern Maternity," presenting plans for rooming-in units. More recently (1946), Maloney, Montgomery, and Trainhaur[4] have stated, "Where mother and baby room together and the mother takes over as much care of the baby as possible, she not only satisfies her driving need to feel useful for her infant, but also, through practice and supervision in the care of the baby, diapering and bathing as well as feeding, she acquires a complete confidence in her ability to care for him and a considerable skill in doing so. She also has an opportunity to know her baby and to learn to interpret his demands for nursing care and how to meet them." These authors also state their belief that the infant, kept at his mother's side,

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†A contribution from Mead Johnson & Company has made possible the services of a full-time pediatric fellow and a full-time nursing fellow.

is safer from infections, gastrointestinal, respiratory, and dermal, than the infant in the crowded hospital nursery.

A point which has been emphasized by the advocates of the rooming-in arrangement is that maternal nursing is readily accepted by mothers who are interested in the advantages of the plan. This is of interest to physicians, who deplore the decline of breast feeding among American mothers.

The psychological as well as the physiological aspects of this question present important considerations. "The first (infantile) needs of the child according to present tenets, are prompt satisfaction of hunger and of the urge to nuzzle and suck, a feeling of warmth and support from nurturing mother, and a peaceful undisturbed rest between times. Accordingly, the very first traumas which can be inflicted upon the helpless infant are a refusal to give him food and comfort when the need for such is indicated, or, conversely, to force food when he is not ready or already has enough. The repetition of such traumatic situations engenders adverse reactions in both parent and child, conducive to subsequent difficulties in the guidance and training of the child."[5]

In considering the present hospital routine separation of mother and infant, it is certain that not only the above needs of the infant have been disregarded, but the fundamental urges of the mother also have been overlooked.

This immediate postpartum period, even though short, certainly can have far-reaching effects, because mothers obviously follow the pattern of infant management as they become acquainted with it in the hospital. The present routine system, where both mother and infant are cared for as separate assignments by separate nurses and often by separate doctors, more often than not presents a somewhat baffling picture to the young mother, who, on leaving the hospital, may know little or nothing about the care and needs of her newborn. In many instances, where artificial feeding has been inaugurated, she may indeed be scarcely acquainted with her baby. A most interesting revelation during the first year's operation of the New Haven Unit has been the reaction of many mothers to rooming-in, in contrast to previous lying-in experience. They not only recalled their feeling of ignorance and helplessness on going home with the baby, but some of them expressed bitterness toward an attitude on the part of physicians who were not interested in maintaining breast feeding.

For the purposes of the present study at the Hospital, mothers were selected in the antenatal clinic, on the basis of their desire to have the baby with them after birth and the desire to nurse. Such mothers, after selection, were interviewed several times by the pediatricians associated with the project at the regular antenatal obstetric visits. At these times, the policies of the unit were explained, the plans for caring for the infant discussed, and questions encouraged. In order to aid in establishing a healthy family relationship, the husband is encouraged to be with his wife during the early part of labor and after delivery to go to the unit for a brief bedside visit. He may hold the baby at this time, after washing his hands and putting on a hospital gown. This practice may be carried out at each of his daily visits during the eight-day stay at the hospital. He may even learn diapering and aid in adjusting the baby to feeding, if the infant demands feeding while he is present.

The New Haven Unit is so arranged that there is a complete twenty-four-hour nursing coverage. Thus, the mother is free at any time to request care for herself or the baby, when needed. The baby may be moved to the adjacent cubicle-nursery also at any time, according to the mother's desire. Visitors to the patient in the unit are restricted to two people in addition to the husband, and only one may be present at a time. Not only is the infant on a demand feeding or *ad lib* schedule, but the mother is, also, to the extent that she need not be roused for many of the usual hospital routines. The unit is attractive, quiet in atmosphere, and has a soundproof ceiling.

From the obstetric viewpoint, two things are of particular interest in reviewing the experience of this plan of hospitalization: first, the maternal nursing which has been fostered in these patients and, second, the mother and infant and family relationships which have been promoted. Recently Dr. Robert L. Jackson[6] has emphasized six important advantages, both to the child and to the mother, in breast feeding infants:

1. Lower mortality and morbidity rates for breast-fed infants, as compared with artificially fed infants.
2. Human milk has a higher nutritional value.
3. Convenience and economy.
4. Lowered incidence of allergy.
5. Earlier involutionary processes in the mother after the termination of pregnancy and the lowered incidence of carcinoma of the breast in women who have nursed their children.
6. Emotional satisfaction, which is very important in establishing parent-child relations.

During the year ending Oct. 29, 1947, 192 mothers and 193 infants (one set of twins) were admitted to the unit. At the time of this writing, 190 obstetric records of these mothers are available for review. Of these 190 patients, 102 were primiparas, 81 multiparas, and in seven the number of pregnancies was not recorded. In studying the age groups, we find that 10 patients were 19 years or less, 133 ranged between 20 and 29 years, and 44 were in the 30- to 39-year group. Two patients were more than 40 years of age and in one instance the age was not recorded. Fifteen of the patients were Negro, the remainder white. Of the 190 patients, 122 delivered spontaneously, 57 with outlet, low, or midforceps, 6 by cesarean section, 4 by breech extraction, 1 private patient not recorded. Not all of the 190 patients had full hospitalization in the unit, because patients are admitted as beds become available after delivery. The great majority of patients (166), however, spent the entire period of hospitalization in the unit.

The review of breast feeding in the group shows that only twelve patients did not nurse their infants in the hospital. In two of these, inadequate nipples prevented nursing and in ten nursing was not desired by the patient, or was prohibited for medical reasons. In the 178 patients who did nurse their infants from birth, the length of time this was continued was variable. In the present study the concern was whether or not breast feeding had continued to the time

of the sixth week postpartum visit. According to the record, 84 patients were continuing to nurse beyond the end of this six-week period; 6 patients nursed their infants for one week or less, and all had given up because of inadequate milk supply. Forty-six patients nursed from one to six weeks. Fifteen failed to return to the clinic for obstetric check-up and in 29 there is no record as to the duration of breast feeding. In 18 of the latter, delivery was by private physicians and information has not been received from them.

There was little demonstrable effect of the Plan on the postpartum physiology of the generative tract. At the time of discharge from the hospital, 31 patients were thought to have some degree of subinvolution and in 15 of these the administration of ergotrate was ordered. Lochia was recorded as somewhat profuse in 9 patients and 2 of these passed small flecks of tissue on the fourth day. We were unable to draw any definite conclusions as to whether involution was increased or lochia was lessened in these patients over patients having the usual type of hospitalization.

During the last three months of the period covered in this review, an earlier type of ambulation was instituted in the unit. In 54 patients, who were completely ambulatory at least three days prior to their discharge from the hospital, there were no observable ill effects. In relation to unit procedure, however, early ambulation effected changes not measurable in statistical terms but nevertheless quite real. Those patients who were allowed to be up and about early in the puerperium were far more likely to feel both able and anxious to take over a considerable part of the infant care than had those whose activities had been limited by confinement in bed. In the young mother with the first child, this seems particularly desirable for reasons that have been pointed out previously.

One of the speculative aspects of the Plan has been the question of the health of the infant kept in the unit as opposed to those kept together in the newborn nursery. Our experience during this first year has been gratifying and interesting. None of the infants developed any of the usual nursery infections. One child had a number of watery stools but this condition cleared rapidly. One infant had a minor skin infection.

The primary purpose of this communication is to acquaint obstetricians with the fundamental considerations of the rooming-in plan and, from an obstetric point of view, to comment upon a year's experience with a four-bed unit. In summary the following points are supported:

1. It seems likely that there will be an increased demand for this kind of hospitalization on the part of both the laity and the profession.
2. The ways in which such demand can be met may involve changes in present hospital and nursing arrangements and in planning for new construction. Some hospitals at present are planning for both rooming-in and regular nursery care.
3. From the obstetric viewpoint, the experience at the Grace-New Haven Community Hospital does not appear to have any disadvantages as far as the health of the mother and child is concerned. Among the impor-

tant advantages are a natural mother and child and family relationship, and the emphasis on the values of breast feeding, and the self-demand schedule.

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HISTOCHEMICAL STUDIES ON THE SECRETION OF MUCUS BY THE HUMAN ENDOCERVIX*

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THE periodicity of mucous secretion by the human endocervix is a well-established phenomenon. Séguy and his co-workers[1, 2] reported an increase in the amount and a decrease in the viscosity of the mucus secreted by the cervix during the midportion of the menstrual cycle. Furthermore, these authors showed by the determination of urinary estrogen and by the examination of the ovaries at operation that the midcycle increase could be correlated with the occurrence of ovulation. More recently, the hormonal control of secretion by the cervix has been demonstrated by the administration of ovarian hormones to ovariectomized women (Abarbanel[3]). The administration of estrogen results in the copious production of clear mucus of low viscosity. Subsequent treatment with progesterone causes a decrease in the volume of mucus secreted and a concommitant increase in its viscosity.

The clinical significance of the changes in the physical and chemical properties of the cervical mucus during the menstrual cycle has been demonstrated by Lamar, Shettles, and Delfs.[4] These authors have shown that the penetrability and longevity of spermatozoa are significantly greater in mucus obtained at the midcycle than in mucus obtained during other phases of the cycle.

The nature and extent of concurrent histologic changes in the endocervix similar to those exhibited by the endometrium have not been satisfactorily established. The opinion of Schröder[5] that it is difficult to detect cyclic changes in the endocervix because of the great individual variability seems to be representative of the earlier workers.

More recently, however, Wollner[6-8] has described cyclic histologic changes of an extensive nature. The method used in obtaining the tissue may have been a factor in his observations. Wollner used an electrocautery to remove strips of tissue about 4 mm. thick, several biopsies frequently being taken from the same individual during a single cycle. Subsequent study of tissue so treated in the living state does not necessarily give information comparable to that obtained from tissue removed by surgical incision. According to the observations of this author there is a complete desquamation of the surface mucosa and widespread destruction and exfoliation of the glandular epithelium during the menstrual phase. During the early proliferative phase rapid regeneration of the epithelial elements takes place, the newly regenerated epithelium being composed of low columnar cells containing relatively little cytoplasm. Throughout the remainder of the cycle the epithelial cells are said to increase in height and the glands to increase in number and size, the peak of development being reached shortly before menstruation.

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In a subsequent extensive survey of the problem, Sjövall[9] disagreed with the findings of Wollner on two major points. First, he believed that the peak of endocervical development is reached at the midcycle and not during the premenstrual phase; second, he observed no widespread desquamation during the menstrual phase. He reported an intensive proliferation of the epithelial elements during the first half of the cycle which reaches its culmination at the time of ovulation. A partial regression was said to take place shortly before and during menstruation.

A new approach to the problem is suggested by the work of Wislocki and associates[10] in which histochemical techniques have been used for the identification of mucin and other constituents of the cervical glands and their secretion. The emphasis of their study was on the nature of the substances present. Since the specimens were not timed with respect to the menstrual cycle, these authors were not concerned with the problem of cyclic change.

The present investigation was undertaken with the purpose of studying by histochemical techniques the production of mucus by the cervical glands during the menstrual cycle and to observe any correlations with the endometrial cycle.

Materials and Methods

In order to secure prompt fixation, material was obtained from patients undergoing total hysterectomy. Samples of tissue of endometrium and of endocervix were removed and fixed immediately. The microscopic study of the endometrium provides a more reliable index of the stage of the cycle than does the meager menstrual history usually given by the patient. It is almost impossible to obtain completely normal tissue from the age groups undergoing surgery. In this series all cases with cervical or endometrial lesions or with demonstrable ovarian endocrine dysfunction were rejected. Of more than 60 cases examined, only 21 are included as being normal. The majority of these uteri were taken from women in the later reproductive age group whose chief complaint was the presence of uterine fibromyomas.

The uteri were received from the operating room shortly after surgical removal. The uterus was opened and the amount of mucus in the cervical canal was estimated on a comparative basis. Cervical specimens were fixed in chilled picro-alcohol-formol (PAF) to preserve the mucin. Tissue from other portions of the reproductive tract was fixed in Bouin's fluid for subsequent diagnostic study.

The tissues were imbedded in paraffin and were sectioned at 10 micra. Sections of cervices fixed in PAF were stained by the Bauer-Feulgen technique which demonstrates the presence of both glycogen and mucin (glycoprotein). In order to differentiate these substances, parallel sections were incubated with saliva to remove glycogen before staining. To spot-check the efficacy of this method, the mucin in occasional sections was also stained metachromatically with toluidine blue. The cervical and other tissue specimens fixed in Bouin's fluid were stained with hematoxylin and eosin.

Observations and Discussion

In nonpregnant women of childbearing age the endocervical mucosa is several millimeters thick. Its surface epithelium, which may exhibit considerable folding, is continued into numerous branched glands. Both the surface and glandular epithelia are composed typically of a single layer of tall columnar cells with basally situated nuclei and clear apical cytoplasm. The glands lie in a rather dense fibrous stroma, the entire mucous membrane resting directly on the dense stroma of the cervix.

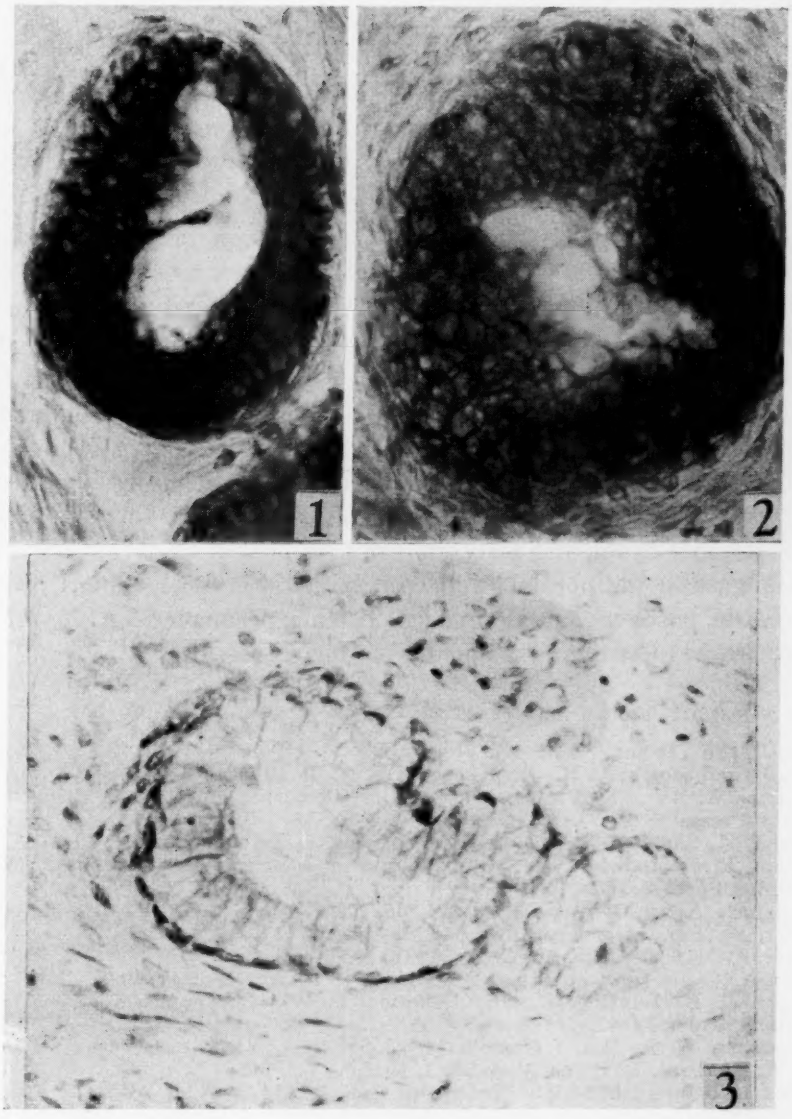
The striking histologic feature in our series of cervices obtained at various stages of the menstrual cycle was the individual variation, particularly in the number and size of cervical glands, which was apparently unrelated to the menstrual cycle. The variability between patients in the pattern of the cervical mucosa is as marked as the extreme variability in the pattern of human mammary gland. Due to the comparatively small number of cases, no attempt has been made to study the minute cytologic detail which was recorded by Sjövall.[9] However, evidence from our specimens agrees with the conclusion of Sjövall that there is no indication of the widespread menstrual exfoliation of surface and glandular epithelium described by Wollner.[6-8]

The results obtained from the tissue sections stained specifically for mucin are informative. At all times throughout the cycle mucin is present in the apical cytoplasm of a large majority of the cells of both the surface and glandular epithelia (Figs. 1 and 2). There seems to be relatively little variation in mucin concentration as judged by the intensity of staining. However, there is a definite variation in the amount of mucin-containing secretion present in the glandular lumina at different phases of the cycle. Lumenal mucus is abundant during the late proliferative and early secretory phases. There is a considerable decrease in the amount present during the late secretory, menstrual, and early proliferative periods. This histochemical evidence of increased secretory activity during the ovulatory phase of the cycle correlates well with the gross observations of Séguy and his co-workers previously referred to. Furthermore, the present observations tend to confirm the conclusion of Sjövall, based upon the degree of papillary excrescense exhibited by the glandular epithelium, that the peak of endocervical activity is reached at the midcycle and not during the premenstrual period as stated by Wollner.

It is also of interest to note that, unlike the goblet cell of the intestinal mucosa, no cellular destruction accompanies the release of mucous secretion in the cervix. The secretory products appear to pass through the intact free surface membrane of the cervical gland cell without an accompanying decrease in cell volume. This indicates that the elaboration and release of mucus is a continuous metabolic process during periods of active secretion. Chemical analysis has shown that not only does the total quantity of mucus increase at the midcycle, but its relative water content also increases (Pommerenke[11]). These analytical and histochemical observations confirm the suggestion that the secretion-promoting action of estrogen may be due, at least in part, to its effect on uterine water metabolism.

During pregnancy the cervical glands increase markedly in size, so much so that the stroma of the mucous membrane is compressed into thin interglandular partitions. The apical cytoplasm of the cells of the surface and glandular epithelia and the glandular lumina contain large quantities of intensely staining mucus. This finding is in complete agreement with the observations of Wislocki and associates.[10] Studies on the physical nature of the mucus during pregnancy indicate that it is not free running but forms a semi-solid plug in the cervical canal (Clift[12]). Little is known regarding the factors responsible for this change in physical character, although a clue may be afforded by the observation of Abarbanel[3] that progesterone causes a decrease in volume and increase in the viscosity of cervical mucus.

After the menopause the cervical glands decrease in size and the glandular epithelium, although of the columnar type, seems to be reduced in height. In accordance with the findings of Wislocki and his co-workers, little or no mucin was present in either the gland cells or lumina of our specimens (Fig. 3). It is apparent that cervical secretion sharply decreases following the cessation of ovarian activity.



Photomicrographs (X 450) of transverse sections of uterine cervical glands treated by the Bauer-Feulgen method to demonstrate mucin. Cellular structure is indistinct since no other cytoplasmic counterstain has been used.

Fig. 1.—Typical cervical gland from a uterine specimen obtained on the first day of menstruation. The cytoplasm of the epithelial cells is filled with intensely stained mucin. Only traces of mucin are present in the lumen.

Fig. 2.—Cervical gland from a uterus removed fourteen days after the onset of menstruation. The endometrial diagnosis was that of late proliferative phase. Moderate to intensely staining mucin is present in both the epithelial cytoplasm and lumenal secretion.

Fig. 3.—Gland from the uterine cervix of a woman whose last menstrual period occurred seven years previous to operation. No mucin staining is present.

The present cytochemical observations on the production of cervical mucus are, for the most part, in close agreement with the gross and chemical findings of other authors previously discussed. However, unlike Pommerenke,[11] we have found no evidence of glycogen in either the surface and glandular epithelium or in the lumenal mucus itself. Several possibilities exist which may account for this divergence of results: (1) the polysaccaride isolated by Pommerenke may not be glycogen; (2) if glycogen, it may be a contaminant from either the endometrial or vaginal secretions; (3) the cytochemical test for glycogen used in the present work may not be sufficiently sensitive to indicate the relatively small quantities reported to be present. That the first alternative is most probable is suggested by the observations of Shettles and Dische.[13] These workers have found evidence that the main bulk of the polysaccarides in human cervical mucus is either identical with or closely related to one of the blood group substances.

Summary

The secretion of mucin by the glands of the human uterine cervix has been studied cytochemically throughout the menstrual cycle. Relatively constant quantities of mucin are present in the apical cytoplasm of the cells of the glandular epithelium at all stages of the cycle. However, active secretion of this substance is a rhythmic process. Large amounts of mucin are liberated during the midcycle, whereas relatively little secretion is found to occur during the late secretory, menstrual, and early proliferative phases.

In contrast to the normal cyclic cervix, little or no mucin is produced in the cervices of postmenopausal women. During pregnancy, on the other hand, there is a marked increase in the amount of mucin present.

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DIAGNOSIS AND TREATMENT OF ANEMIA OF THE NEWBORN CAUSED BY OCCULT PLACENTAL HEMORRHAGE

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THE hazards to the mother of hemorrhage caused by abruptio placentae and placenta previa are well known, but while it is generally recognized that such cases are attended with high fetal mortality rate due to asphyxia, little or no cognizance is ordinarily taken of the fact that infants born alive in such cases or even in apparently normal deliveries may be suffering from a dangerous anemia due to occult hemorrhage from the placental or umbilical vessels. One reason for this may be that such severe neonatal anemias closely simulate the hemolytic anemia of erythroblastosis fetalis, so that these infants are usually treated like erythroblastotic infants. Undoubtedly many infants who might otherwise have been saved have been lost due to failure to recognize the true nature of the condition, considering that severe posthemorrhagic anemia, which is often associated with shock, calls for much more vigorous transfusion therapy than hemolytic anemia. Now that exchange transfusion[1, 2] has come to be used almost routinely in cases of erythroblastosis due to Rh sensitization, it is even more important to distinguish posthemorrhagic anemia, because the former is best treated by simple, massive blood transfusions rather than by exchange transfusion. The development of serologic tests[3-6] whereby the presence or absence of erythroblastosis can be determined with an accuracy approximating 100 per cent has simplified this problem, especially if antenatal Rh tests are performed routinely. In cases where the mother is Rh positive, or, if Rh negative, has neither anti-Rh agglutinins nor glutinins in her serum, the diagnosis of erythroblastosis can be excluded, as a rule,* raising in its place the question of a possible posthemorrhagic anemia.

The purpose of this paper is to present cases of severe anemia of the newborn infant due to occult placental hemorrhage, and to discuss the differential diagnosis and treatment of the condition.

Reports of Cases

CASE 1.—On Aug. 5, 1947, the author was requested to see the patient, a female newborn infant, because it was noticed at delivery that the infant looked extremely pale and had very low vitality.

The mother's obstetric history was as follows: Her first pregnancy, in 1942, had terminated with a seven-month stillbirth, the cause of which was not determined. The second pregnancy, in 1944, had terminated with a full-term natural delivery of an infant weighing 6 pounds, twelve ounces, who was apparently normal and is alive and well. The patient with whom we are concerned here was the result of her mother's third pregnancy. This baby was delivered by cesarean section because of a central placenta previa, and the obstetrician noticed

*This does not take into account the possibility of A-B sensitization, or other rare sensitizations.

that the cord pulsations were weak. Because of the baby's pallor, an immediate blood count was done, and this revealed a hemoglobin concentration of 8.7 Gm. per cent (67 per cent), with a red cell count of 2.5 million per cubic millimeter.

An antenatal Rh test had been performed on the mother, which showed her to be Rh positive, and this fact, together with the existence of a central placenta previa, suggested the idea that the baby might be suffering from anemia and shock due to occult hemorrhage from the fetal surface of the placenta. Fetal hemorrhage of this type would not be manifest because the fetal blood would be mixed with the maternal blood lost at the delivery. A transfusion of 120 c.c.* of citrated group A blood was given with the aid of a syringe-valve apparatus, and the infant immediately improved. The following morning a blood count revealed a hemoglobin concentration of 11.7 Gm. per 100 c.c. (81 per cent); red blood cells, 4.35 million per cu. mm.; white blood cells, 41,200 per cu. mm.; with 52 nucleated red blood cells per 100 white cells on smear. The same evening a blood count showed a hemoglobin concentration of 16 Gm. per 100 c.c. (110 per cent). This improvement was maintained, and on the following day the hemoglobin concentration was 14.9 Gm. per 100 c.c. (103 per cent); red blood cells, 4.7 million; white blood cells, 32,400; polys, 65; band forms, 10; lymphs, 19; monos, 2; eos, 4; with only 2 nucleated red blood cells per 100 white cells.

Despite the sustained improvement in blood count, the baby looked pale, and oxygen had to be administered, because the respirations became rapid and shallow whenever the oxygen therapy was discontinued. This indicated that while the blood count was satisfactory, the blood volume was still probably below normal. On the following day, August 8, the hemoglobin concentration was 13.3 Gm. (92 per cent); red blood cells, 4.55 million; white blood cells, 17,600; and a transfusion of 60 c.c. of blood was given. Following this transfusion the hemoglobin concentration rose only to 14.5 Gm. (100 per cent), but the patient improved markedly so that the oxygen therapy was no longer necessary, which confirmed the idea that reduction in blood volume was the cause of the symptoms. The patient was discharged from the hospital in good condition, and when she was seen again on August 28 she appeared entirely normal, and the blood count showed hemoglobin concentration 10 Gm. (76 per cent); red blood cells, 4.09 million; white blood cells, 18,200; polys, 33 (1 band form); lymphs, 60; monos, 3; eos, 3; with ½ per cent reticulocytes and no erythroblasts on the smear.

As has already been mentioned, the first clue to the correct diagnosis in this case was provided by the antenatal Rh test which showed the mother to be Rh positive. The results of more complete tests performed later on are shown in Table I.

TABLE I

BLOOD OF	GROUP AND SUBGROUP	M-N TYPE*	RH-HR TYPE
Mother	A_2B	N	Rh_1rh
Patient (female infant)	A_2	MN	Rh_2

*The M-N types are not clinically significant but are included for the sake of completeness.

The second lead was supplied by the history of central placenta previa, which is usually characterized by profuse placental bleeding. In addition, physical examination of the infant showed that neither spleen nor liver were enlarged, while if such severe anemia were due to hemolysis, considerable enlargement of these organs should be present. Moreover, the icterus index of the cord serum was only eight units. Undoubtedly, this child owes her life to the prompt and adequate transfusion therapy which she received.

CASE 2.—The patient was a newborn, full-term, female infant, weighing 6 pounds, 10 ounces, who was born at 3:15 A.M. on Feb. 8, 1947. The infant was the first born to her mother, who had never received a blood transfusion and was known to be Rh positive, group O from antenatal tests. Labor had been normal and was completed with an easy outlet forceps.

*About twice the usual dose for an infant weighing 7 pounds or less.

The infant cried spontaneously, and respirations were good at first, but it was noticed that she was very pale. There were no evident anatomical anomalies, no edema; and meconium and urine passed by the infant appeared normal. An immediate blood count showed: hemoglobin concentration, 6.5 Gm. per 100 c.c. (45 per cent); red blood cells, 2.21 million; white blood cells, 57,000; polys, 27; juveniles, 4; myelocytes, 3; lymphs, 55; eos, 2; monos, 4; unidentified cells, 3; with 59 nucleated red cells per 100 white cells on the smear.

While the diagnosis of erythroblastosis fetalis seemed to be excluded by the facts that the infant was the first born and her mother Rh-positive, this patient was seen before the infant of Case 1, and the true nature of the condition was not fully appreciated. The infant was given continuous oxygen therapy and vitamin K. At 4:30 A.M. the infant ceased breathing, but the heart action continued. Because of the infant's desperate condition, 100 c.c. of blood were drawn from the mother, mixed with 20 c.c. of Witebsky's A and B group substances, and transfused to the infant. Following this, the infant rallied, she cried weakly, and spontaneous breathing was resumed. This improvement was only evanescent, however, and at 5:30 A.M., the infant expired.

In retrospect, it seems evident that despite the apparently normal delivery, this infant was suffering from posthemorrhagic shock caused by occult placental bleeding. Had this patient been seen after Case 1, the true nature of the condition might have been recognized, and the infant might have been saved by more energetic transfusion therapy. As already mentioned, the only clues to the true nature of the condition available to us were the facts that the infant was first-born, and her mother was Rh-positive. Results of more complete blood tests performed later on are shown in Table II. Direct matching, by the agglutination and conglutination methods, of the maternal serum against the blood cells of the infant and her father showed no clumping, confirming the impression that the mother was not isosensitized. Moreover, the icterus index of the cord serum was only four units, which further excluded the presence of any hemolytic process.

TABLE II

BLOOD OF	GROUP	M-N TYPE	RH-HR TYPE
Father	0	MN	Rh_1Rh_2
Mother	0	MN	Rh_1Rh_1
Patient	0	MN	Rh_1rh

At postmortem examination, the findings noted by the pathologist were anemia, hepatosplenomegaly, extramedullary hematopoiesis in the liver, adrenal glands and spleen, atelectasis of the lungs, and focal congestion of the viscerae. The only diagnosis ventured by the pathologist was "a newborn with anemia."

CASE 3.—This is an unusual case of erythroblastosis which is included for purposes of comparison with Cases 1 and 2, because of certain of its features which are relevant to the problem under discussion.

The patient was a female infant, born on March 31, 1947 at 1 A.M., the result of her mother's third pregnancy. The patient's mother gave the following obstetric history. Her first pregnancy terminated with an incomplete abortion which was treated by curettage on March 24, 1942. The second pregnancy yielded a full-term female child, who was born on February 18, 1943. This infant developed a hemolytic anemia and was treated by numerous transfusions of Rh-negative blood, and finally recovered completely at the age of six weeks. This child is alive and well, without any sequelae of erythroblastosis. The patient's mother was first seen during her third pregnancy on Sept. 15, 1946, when she gave her last menstrual period as June 18, 1946, with an E.D.C. of March 25, 1947. At this first antenatal examination, grouping and Rh-Hr tests gave the results seen in Table III.

As expected, these results showed the mother to be Rh negative and the father to be Rh positive. Moreover, the father was Hr negative (indicated by the designation Rh_1Rh_1), so that

he belongs either to genotype R^1R^1 or to genotype R^1r', of which the former is by far the more common and therefore the more probable. It will be noted that the living child, who recovered from erythroblastosis, belongs to type Rh_1rh, in conformity with expectations. In view of these results there was hardly any doubt that the fetus the mother was carrying would also be Rh positive.

TABLE III

BLOOD OF	GROUP AND SUBGROUP	M-N TYPE	RH-HR TYPE	
			PHENOTYPE	GENOTYPE
Father	A_1	MN	Rh_1Rh_1	R^1R^1 of R^1r'
Mother	A_2	MN	rh	rr
First child	A_1	MN	Rh_1rh	R^1r

Tests for Rh antibodies on the maternal serum at the time of this first antenatal examination gave the following results:

Agglutination method = negative
Albumin-plasma conglutination method = negative

Thus, whatever sensitization the mother had possessed at the time of her second pregnancy had subsided in the interval of more than three years until the present pregnancy began.

The Rh antibody titrations were repeated on Dec. 20, 1946, Feb. 15, 1947, and on March 15, 1947, and at all these examinations no Rh antibodies were demonstrable in the maternal serum. The mother was being counterimmunized with typhoid and pertussis vaccines, and these results we ascribed to the successful use of the vaccines and were lulled into a false sense of security as subsequent events soon revealed.

When the patient was born on March 31, 1947 at 1 A.M., she proved to be extremely pale and feeble; she gave only one good cry and then breathed poorly. Much mucus was aspirated from her throat, and an immediate blood count showed a hemoglobin concentration of only 7.4 Gm. per 100 c.c. (58 per cent), with 3.09 million red blood cells per cu. mm.; white blood cells, 46,500; polys, 15; bands, 3; small lymphs, 58; large lymphs, 20; monos, 1; eos, 1; baso, 1; myelocytes, 1; and there were 25 erythroblasts and 17 normoblasts per 100 white cells on the blood smear. A blood transfusion was obviously urgently indicated, and this was started at 5 A.M., by which time the infant's condition was critical. After a total of 90 c.c. of group A, type rh blood were transfused, the infant died and could not be revived. In cutting down at the ankle to expose the vein for the transfusion, it was noticed that the tissues were bloodless, and the vein was found to be empty and fragile, so that only with the gentlest handling was it possible to cannulate it and start the transfusion. Physical examination revealed the spleen to be hard and markedly enlarged, and tests performed later on revealed the baby's blood type to be group O, type M, type Rh_1rh, while the icterus index of the cord serum was only 10 units. Another blood specimen was drawn from the mother at the time of delivery and this showed the presence of anti-Rh_0 agglutinins of 16 units titer. Still another specimen obtained from the mother about two weeks after the delivery showed the presence of anti-Rh_0 agglutinins of a titer of 128 units.

At postmortem examination, the characteristic findings of erythroblastosis were noted. There was marked hepato-splenomegaly with microscopic evidence of extensive erythropoiesis and some myelopoiesis. In addition, the liver cells were filled with hemosiderin pigment. Other incidental findings noted were aspiration of amniotic contents, and a small hematoma of the arch of the aorta.

This case is unusual because antenatal tests repeated at intervals up to two weeks before delivery failed to reveal the presence of any Rh antibodies, yet the infant proved to be erythroblastotic. The explanation for the presence of erythroblastosis in the infant was provided by another antibody test on the maternal serum at delivery which then revealed the presence of Rh antibodies. The moral of this case is that in the face of an obstetric history of erythroblastosis in a

previous child, one must not be lulled into a false sense of security by failure to demonstrate Rh antibodies in the maternal serum. In all such cases, the transfusionist should stand by at the delivery prepared to transfuse the infant if necessary. Apparently something must have happened in the interval of two weeks between the last antenatal examination and the delivery which caused the sudden rise of maternal Rh antibody titer and the appearance of the severe anemia in the infant. Had labor been induced two weeks before term, the outcome in this case might have been entirely different. Incidentally, this case also shows the relative ineffectiveness of counterimmunization with typhoid and pertussis vaccines in a seemingly ideal case for the application of this treatment. While there is ample experimental data to support the principle of competition of antigens, it does not seem likely to lead to an effective prophylactic treatment against erythroblastosis.

The simplest way to account for the findings in this case would be to postulate some defect on the fetal side of the placenta, appearing during the two-week interval between the last antenatal Rh antibody titration and the delivery of the patient. The leakage of the fetal blood into the maternal circulation would account for the sudden reappearance of Rh antibodies in the maternal serum. Moreover, a slow ooze of fetal blood from such a placental defect could also account for the extreme anemia and shocklike condition of the infant at birth. The main objection to this concept is the difficulty of demonstrating such postulated placental defects in pathologic specimens. However, the reason for this may be that such defects need not be large, and as a rule would probably be demonstrable only in vivo, as we succeeded in doing another case recently seen by us. In this other case, the baby was delivered by cesarean section, and at the operation a herniation was found of the anterior uterine wall (due to a previous cesarean section), consisting of a sac about the size of a walnut, and lined only by peritoneum and filled with blood, which ruptured upon palpation.

The importance of this interpretation is that when erythroblastotic babies are born with extreme anemia and shock one must consider the possibility that the anemia may be due not merely to hemolysis but also to actual blood loss through a placental defect. The correctness of this concept as applied to the case reported here seems indicated by the normal icterus index of the cord serum. Under this concept, such infants are best treated by simple but massive transfusions of Rh-negative blood, as in a case previously reported by the writer.[7] If exchange transfusion therapy is applied in such cases, a margin of about 150 c.c. (instead of 50 c.c.) should be maintained between the volume of blood injected and the volume of blood withdrawn, in order to correct the reduction of blood volume produced by the inapparent placental bleeding.

Comment

Related to the problem under discussion is the clinical entity known as vasa previa, a condition usually associated with a velamentous insertion of the cord. A good review of this subject has recently been published by Rucker and Tureman,[8] who also add three new cases of their own. This complication of pregnancy is not important from the maternal standpoint, but carries with it a high infant mortality rate. Thus, in a series of 52 cases culled from the literature, as many as 58 per cent of the babies died. The babies who lived were mostly delivered through a tear in the membranes between the blood vessels without rupturing the blood vessels. The babies who died were mostly stillborn, presumably due to asphyxia from pressure on the exposed blood vessels, or from shock caused by bleeding in utero from the ruptured blood vessels. Caffarotto[9]

reported three interesting cases of vasa previa: one with stillborn baby, one with an asphyxiated baby that recovered, and one with a baby that died in a few days of anemia. Thus, where the babies are born alive, in occasional cases the babies will have a severe posthemorrhagic anemia, and such babies should be treated by massive transfusion without delay if they are to survive.

Summary

1. Attention is called to a previously unrecognized entity, namely, severe anemia of the newborn caused by unapparent hemorrhage from the fetal surface of the placenta.

2. Two cases are described of newborn infants exhibiting this picture of severe posthemorrhagic anemia, one of whom recovered following treatment by blood transfusion, while the other died despite transfusion. In both these cases the mothers were Rh positive as revealed by routine antenatal blood tests, and isosensitization was ruled out as playing any role by detailed serological tests and the absence of any icterus of the cord serum.

3. In a third fatal case of severe anemia in the newborn baby of a sensitized Rh-negative woman, the anemia was apparently due primarily to hemorrhage rather than hemolysis. The significance of this finding in relation to the treatment of such cases is that if exchange transfusions are given to such erythroblastotic babies, a margin of 150 c.c. instead of only 50 c.c. should be maintained between the amount of blood injected and the amount of blood withdrawn, in order to correct the reduction in blood volume as well as the anemia.

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THE USE OF STILBESTROL IN ABNORMAL GYNECOLOGIC BLEEDING (NONMALIGNANT)

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THE various drug remedies employed, heretofore in the treatment of benign gynecologic bleeding have been largely disappointing, due, perhaps, to improper selection and use of some, and the prohibitive cost of others. In search of such a remedy, therefore, as would yield uniformly satisfactory results and have at the same time an economic appeal, we were impressed favorably with the published results of Karnaky[1] from the use of stilbestrol in oil and undertook the following study.

Cognizant, however, of the criticisms and many questions concerning the pharmacodynamics, for which we had not the answer, and mindful of the possible recriminations aroused by use of this paradoxically acting and potentially carcinogenic drug, we continued its use with satisfaction, as the bleeding was being controlled with unfailing suddenness where other drugs had failed. The progression of anemia was arrested and the woman, relieved of anxiety, returned to her home with the feeling that something had been done for her.

Explanation of the mechanism of stilbestrol, according to Karnaky, is as follows: "At a certain estrogenic hormonal blood level which varies in each individual and locality, a constriction of the spiral arteries of the endometrium occurs. This leads to anemia, dehydration, anoxemia, necrosis, dilatation of the spiral arteries and subsequently to bleeding or menstruation. A woman bleeds or menstruates only when the estrogenic hormones reach a certain blood level, above and below which the woman is amenorrheic regardless of the condition, size, position, shape, or contents of the uterus."[1]

The purpose of this paper is to report our experience and findings in controlling uterine bleeding with stilbestrol* in our hospital and out-patient services and to point out certain worth-while observations.

Clinical material for this study was obtained through the cooperation of our indoor and outdoor staffs, many of whom allowed the records of their private patients to be used in order to increase the scope and evaluation of the report. These patients were unselected and presented themselves invariably because of excessive uterine bleeding.

Following a gynecologic history and vaginal examination, biopsy of the endometrium was taken, followed by an injection of stilbestrol (25 mg. per c.c. in oil) into the anterior lip of the uterine cervix. The patient was then allowed to go home and, on the next morning, the following determinations were made: basal metabolic rate, bleeding time, coagulation time, and hemoglobin. If, at

*Acknowledgment with thanks is hereby made to the Winthrop Chemical Company, The Abbott Company and The Burroughs Wellcome Company for supplying the drug material for this study.

this time, bleeding had ceased, no further stilbestrol was given, but thyroid extract was administered as indicated by the basal metabolism rate determination. These patients were seen routinely forty-eight hours later, when more stilbestrol was given if indicated.

This investigation comprises well over 200 cases which were controlled satisfactorily by the use of stilbestrol as noted. In sixty cases for which adequate follow-up was available, there were definite trends which we believe are of sufficient importance to consider in detail. Of these, 74.2 per cent required only one injection of stilbestrol to control the bleeding; 9.7 per cent, two injections, and 13 per cent required three. The remaining 3.1 per cent required four or more injections with supplemental oral administration in 15 mg. doses at bedtime.

TABLE I. STILBESTROL DOSAGES

DOSE (MG.)	NO. OF PATIENTS BY AGES				TOTAL PATIENTS
	10-20	20-30	30-40	40-50	
25	8	40	11	1	60
50		4	2		6
75		5	3		8
100		1			1
125			2		2
150					
200	2	1			3

When the time element was studied, it was noted that 42 per cent stopped bleeding in less than twelve hours and 28 per cent in less than twenty-four hours. Thus in 70 per cent of these women, the bleeding was completely controlled or diminished to a negligible quantum. While bleeding in the remaining 30 per cent was not completely controlled in twenty-four hours, it was markedly reduced in amount.

Despite the large or repeated dosage, no toxic effects were observed of sufficient intensity to cause the drug to be discontinued. Furthermore, no case of estrogen-withdrawal bleeding was encountered in this investigation. We know of no other nonoperative method which gives as favorable results, despite the fact that the approach may seem more rationally scientific.

In 37 of the 60 cases under consideration, the basal metabolic rate determinations indicated decreased thyroid function (in 27, or 70 per cent) ranging from minus 1 to minus 30 per cent. Ten were on the positive side with a similar range (plus 1 to plus 30 per cent). Twenty-three are not accounted for because of various types of patient failures which would have nullified the significance of the determinations.

TABLE II. BASAL METABOLIC RATE

AGE GROUP	MINUS		PLUS	
	NO.	PER CENT	NO.	PER CENT
1-10	13	35.1	6	16.2
10-20	13	35.1	3	8.1
20-30			1	2.7
30-40			1	2.7
Total	26	70.2	11	29.7

Classification of the types of bleeding indicated that 41.2 per cent was menorrhagic; 30.2 per cent, menometrorrhagic, and 28.6 per cent, metrostaxic.

Evaluation of 53 endometrial biopsy studies revealed that the bleeding was associated with a proliferative endometrium in 37 (70.2 per cent). Twelve

TABLE III. TYPES OF BLEEDING

AGE GROUPS	10-20	20-30	30-40	40-50	TOTAL	PER CENT
Menorrhagia	2	19	6		26	41.2
Metrostaxis	1	14	3		18	28.6
Menometrorrhagia	3	8	6	2	19	30.2

specimens (22.6 per cent) revealed the endometrium to be in a poorly differentiative phase. This was true when a correction was applied for twelve reports revealing three submucous leiomyomas, four retained secudines, and five specimens marked unsatisfactory for study. It is interesting that the bleeding was controlled equally as well in these latter cases as in the others. These results became more significant when the age groups were broken down showing that 35 (58.3 per cent) ranged from 20 to 30; 15 (25 per cent) 30 to 40; 8 (13.3 per cent) 10 to 20; 2 (3.3 per cent) over 40.

TABLE IV. ENDOMETRIAL BIOPSY

	AGE GROUP					
	10-20	20-30	30-40	40-50	TOTAL	PER CENT
Proliferative phase	6	21	10		37	70.7
Differentiative phase		10	2		12	22.6
Hyperplasia	1		1		2	3.6
Endometritis		1	1		2	3.6
Submucous fibroid		1	1	1	3	
Retained secundines		4			4	
Specimen unsatisfactory		1	3	1	5	

TABLE V. AGE DISTRIBUTION

AGE	NO.	PER CENT
10-20	8	13.3
20-30	35	58.3
30-40	15	25.0
40-50	2	3.3

Although the majority of these women were in the childbearing period, these bleeding disorders predicated relative barrenness, since 67 pregnancies, a small number for the number of women in this age group, resulted in but 62 childbirths. This is particularly noteworthy since only ten women (16.6 per cent) were in the age groups where pregnancy is undesirable (10-20 years and over 40).

Vaginal examinations revealed that 70 per cent had some type of pelvic disorder evidenced by infection, adnexal masses or tenderness, bleeding fibroids, malpositions of the uterus and its adnexae. Apparently, neither was the effectiveness of the treatment reduced by these disorders nor the amount and frequency of administration of the drug altered thereby.

All of the cases had various phases of anemia but no abnormalities were noted in the bleeding or clotting time of a single case nor evidence of avitaminosis. Hence, no vitamin or liver deficiency studies were made.

In view of the fact that in 70.7 per cent the endometrium was in the proliferative phase, that 70.4 per cent of the bleeding occurred at the normal menstrual period, that the majority of these women had evidence of hypothyroid function, the study indicated that, probably, abnormal ovarian functioning was responsible directly or indirectly for the bleedings.

Furthermore, studies on the follow-up patients are in agreement with the results of others, in that the return of the normal menstrual cycle is not inter-

fered with unless there is some extensive organic pelvic pathology requiring surgical treatment. One such patient (No. 2) who was difficult to manage had a history of functional type of bleeding over a period of nineteen years. At operation, extensive unilateral cystic disease of the ovary was found, despite the fact that at operation nine years previously the ovary was reported to be normal.

Our observations and experience, based on the results of this study during the past three years, warrant the conclusion that the use of stilbestrol as described herein is a safe, economic, practicable, and effective therapeutic agent for abnormal gynecologic bleeding (nonmalignant), not only as a temporary expedient, but as a long-range, satisfactory remedy in a significant number of the cases.

Summary

1. In more than 200 cases, excessive gynecologic bleeding (nonmalignant) was controlled satisfactorily in 99 per cent by the injection of stilbestrol in oil (25 mg. per c.c. dosage) into the anterior lip of the cervix uteri.

2. A critical analysis of 60 cases revealed that 58.3 per cent ranged from 20 to 30 years of age; 70 per cent had decreased thyroid function; 70 per cent had pelvic disorders; 71.4 per cent were menorrhagic and menometrorrhagic; 70.2 per cent bled from a proliferative endometrium and infertility was significantly higher.

3. Large or repeated dosage of stilbestrol did not cause toxic symptoms of sufficient intensity to warrant its discontinuance or modification.

4. The pelvic disorders did not contraindicate such use of stilbestrol.

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RESULTS OF ARTIFICIAL INSEMINATION WITH AN EXTRAMARITAL SPECIMEN (SEMI-ADOPTION)

Report on 89 Cases

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DURING a period of seven years, 83 couples, in whom the wife was appraised as potentially fertile, have applied for semi-adoption on 89 occasions with 66, or 74 per cent, successful results. Fertilization at the first insemination occurred in 21 cases. The immediate psychological reactions were generally gratifying but the ultimate or teleologic results belong to the future.

An itemized list of the successful cases is submitted, showing the menstrual pattern in each case, the day of fruitful insemination, and, in most cases, an accurate record of the carrying time. Certain unique cases are briefly abstracted.

The eugenic, ethical, and biologic ideals which the writer believes essential to this work are presented. No dogmatism is intended, as it is assumed each individual will be governed by his own philosophy. Irresponsible practices may eventually and properly lead to legal restrictions.

The various observations which may guide the attendant in selecting the most favorable day for insemination are discussed in some detail. In computing the day of cycle the writer counts the day after onset of menstruation as one elapsed day.

No immediate or deferred pelvic reaction is known to have occurred in this series. This is attributed to great care in avoiding invasion of the internal os by instrument or seminal specimen.

Because the public has embraced a more intelligent and realistic philosophy concerning sex and eugenics and because greater, and possibly unwarranted, restrictions are imposed upon those seeking desirable offspring for regular adoption, an increasing number of childless couples are consulting physicians regarding the feasibility of fertilizing the wife with an extramarital semen, a procedure which the writer has designated as semi-adoption.

The method has no justification, of course, except in those marriages in which the infertility of the husband is incurable and the innate and compelling urge of the wife to experience reproduction is honored by the mate. Opposition may be based upon the interpretation of ancient, ecclesiastic dogmas or the idea may be opposed in principle by some physicians and their patients. One readily agrees that such considered opinions should be respected but it would seem that couples whose religious, ethical, and social convictions have led to a favorable decision should have access to sympathetic guidance and to responsible care in suitable cases. Artificial fertilization of the female has a relatively long history in husbandry and medicine, but interest in the use of an alien semen for the relief of certain barren marriages was again stimulated approximately a decade

ago, when remarkable results were published in an official medical journal and later exploited in the sensational daily press. Many critical readers believed this report to be unduly roseate and certain claims seemed incongruous with vital statistics.

In response, therefore, to the informal suggestions of a few associates on the National Committee of Maternal Health, your reporter agreed, in 1939, to investigate the biological and psychological results which might be obtained by semi-adoption providing the following ideals could be realized:

1. The husband and wife were to be interviewed and the infertility and cooperation of the husband confirmed. Furthermore, signatures granting permission for the procedure were to be obtained after the uncertainties and limitations of the method were fully explained.
2. Only donors with a normal degree of fertility and with a cultural and eugenic background equal or superior to that of the patients were to be used. Broad racial and religious prejudices were to be satisfied, and, more recently, the Rh factor, when known, was given consideration.
3. Specimens were to be prepared at the office or delivered promptly from a short distance, thus aiming to avoid any unknown changes that might result from aging or artificial preservation of the semen.
4. Adequate examinations giving reasonable assurance of the wife's fertility were to be made and insemination deferred pending the correction of poor health, hypothyroidism, habitual menstrual irregularities, or other inhibitory factors.
5. Patients were to be accorded complete privacy and were to cooperate with plans to assure no possible meeting or identification between donor and patient. This was accomplished by having patients contact the office from a near-by telephone for instructions ten minutes before their appointment.
6. Patients with little hope of successful issue or those planning to supply their own donor were to be promptly discouraged.

The results seem to have justified this onerous but precautionary program.

Biologic Results

In a period of approximately seven years, 83 couples, in whom the wife was appraised as potentially fertile, applied for artificial insemination on 89 occasions, with successful results in 66 cases. Pregnancy followed the first insemination in 21 instances. In order to avoid the basic criticism directed toward some previous statistics and to provide a complete clinical picture, it should be stated that seven pregnancies terminated as miscarriages and there was one mole and one ectopic gestation. In the opinion of the writer, these complications were not at variance with normal expectations. A new donor had been used in the case of placental degeneration and, because of a personal bias rather than any scientific conviction, this specimen was not employed again. It is possible the ectopic might have been avoided had the physician's advice prevailed. This talented and determined wife gave a previous history of many unsuccessful trials of artificial insemination. The adolescent and mature records were not explanatory but the uterus was sensitive and in advanced retroversion. Reposition and pessary support were ultimately accomplished and a favorable uterine secretion was demonstrated concomitant with the estimated period of high follicular activity. Immediate success and an uneventful delivery followed the first insemination. This enthusiastic patient returned a few months later with a postpartum

retroversion and some signs of incomplete involution. The displacement was readily supported and she refused to defer insemination pending more complete involution. The first trial was again successful but terminated in a salpingo-oophorectomy for tubal pregnancy. Without critical comment and ignoring a doubtful prognosis, she requested insemination the following year and was successfully delivered.

Psychological Results

The psychological results must be estimated by the reaction of couples with varying temperaments and articulative abilities. The ultimate or teleologic results belong to the future and are as unpredictable as human destiny. The contemporary reactions of these patients seem to have been universally gratifying and, in several instances, the husband made a special effort to register his appreciation. Temporary anxiety was exhibited by one wife delivered more than two weeks after the estimated date of confinement. She and her husband had practiced contraception simultaneously for years (condom and vaginal diaphragm) to avoid reproduction, because a serious physical deformity had occurred in every traceable generation of the husband's family. She feared that the late delivery might indicate failure of contraception rather than successful insemination.

Failures and Deferred Successes

Each couple was informed at the outset that obscure and variable factors were involved and they must anticipate the possibility of failure. Experience has seemed to demonstrate that a less favorable prognosis should be entertained when three or four inseminations, conducted under favorable indications, have failed. Under the latter circumstances, a few patients applied for full adoption, while many others accepted failure stoically and apparently found satisfaction in having made every practicable effort. Only four couples elected to plan for more than eight trials, and three ultimately terminated successfully on the ninth, twelfth, and twenty-first inseminations, respectively.

The first of this triad was a small, asthenic, and cultured girl with low blood pressure, a metabolism of minus twelve, and a cervical stenosis which evidently followed an earlier cauterization for erosion and discharge. After six trials, the attending gynecologist, in another city, cooperated by performing a premenstrual dilation and light curettage. A mature, secretory endometrium was reported. Thyroid therapy was resumed and, after several weeks, two inseminations in one cycle proved efficient. After an early threat of miscarriage she was successfully delivered. The second patient was a thin, tense, but apparently healthy girl who menstruated every 24, 25, or, less frequently, every 26 days and presented no anatomic or metabolic disturbances. In our general, clinical study of female sterility, we have found that patients of this type belong to a low-fertility group; and, from an extensive experience in the study of vaginal smears, Papanicolaou asserts that women with habitual cycles of every 24 days or less rarely ovulate normally. The third patient was meticulously investigated in office, laboratory, and finally, at her request, under anesthesia at the hospital without revealing any inhibitory factor. The endometrium reflected full follicular evolution but smears were less decisive. In each of these cases, success was finally attained on a day of the cycle and with a specimen that had been repeatedly used without result.

At least nine failures resulted when patients insisted upon the undertaking although disadvantageous factors were present and a less favorable prognosis was given. Experience suggests that minor disorders of the pelvis and lesser seminal defects which would not prevent conception indefinitely under marital conditions assume major significance in artificial impregnation.

Supplementary Statistics

An itemized list of 66 successful cases is presented to show the predominate menstrual cycle, the day on which the fruitful insemination was performed, and the actual number of days which elapsed until delivery. It was believe this last item might be of interest to obstetricians. These data were accumulated by restricting insemination to a single trial in each cycle. Exceptions were made for a few patients who came from very distant points and, therefore, elected two or three trials during a single cycle. The "carrying time" is necessarily omitted in such instances and in a very few additional cases in which the date of delivery was not reported.

In our early experience, it was noted that menstruation of normal patients was sometimes delayed for many days following the initial insemination, which led to false hope and proportionately severe disappointment. One of these patients, a keen psychologist, confirmed our impression that this delay was caused by mounting anxiety as the time of the next period approached; and she suggested that this tension might be relieved if the original contract provided, when necessary, for insemination during three separate cycles and thus gave greater assurance of ultimate success. This plan improved the morale of patients and possibly contributed to the effectiveness of the procedure.

Day of Successful Insemination

For two decades prior to the inception of this study and for some years before the time of human ovulation was generally established, the writer had been studying the cervical secretion in various phases of the menstrual cycle to determine the most favorable time to conduct the postcoital test. In 1930, we published an analysis of 200 postcoital studies and noted that there was an ideal time a few days after the cessation of the period, when the canal of the healthy cervix was distended with a clear, glistening, less viscid mucus which overflowed from the gaping external os into the vaginal vault. This condition, which was called the weeping cervix, evidently favored spermatozoal invasion. It was not, however, until distinguished experimenters had clarified the physiology of ovulation and coordinated it with the menstrual cycle that we recognized the weeping cervix as a manifestation of high follicular activity and impending ovulation. By the experience gained in correlating the time of this phenomenon with the length of the cycle, it was often possible, after reviewing the menstrual pattern of the prospective patient, to predict the most propitious time for insemination with fair accuracy. In other so-called regular patients, there was sufficient variability in the cycle to introduce an element of chance. It is significant that typical hypersecretion of the cervix was present at the time of insemination in every case in which conception followed the first insemination.

In reviewing the cases, it appears that the fruitful inseminations were performed one or two days earlier than the generally accepted time of ovulation. The same observation was reported by Rock in a personal communication. In this series, for instance, 56 pregnancies could be definitely credited to a single insemination per cycle and, of these, 17 were recorded on the eleventh and 13 on the twelfth day of the cycle. These two days, therefore, account for nearly one-half of the total conceptions and for approximately 70 per cent of the pregnancies occurring in women who menstruated every 27 to 29 days. Four fertilizations were secured on each of days 13 and 15 of the cycle and five on the fourteenth day, the latter days being selected for patients who flowed every 30 to 32 days. One patient with a cycle of 34 days responded on the sixteenth day. Insemination proved effective on the tenth day on 10 occasions and included many patients with

TABLE I. ITEMIZED LIST OF PREGNANCIES

NO.	AGE	TYPE OF CYCLE	DAY OF INJECTION	DAYS IN UTERO
1	25	33-35	16	278
2	25	26	11	
3	34	25-29	9-11-12	
4	34	27-29	12	269
5	34	28-30	15	261
6	25	27-32	14	271
7	23	27-28	12	
8	36	28-30	12	282
9	23	28	2d week	
10	31	28	11-12	
11	30	30	12	278
12	26	31-34	16-17	
13	27	28	13	263
14	26	28-33	11	277
15	23	33-35	15	262
16	30	28-30	12	
17	37	28	11	
18	30	26-27	11	259
19	32	23-26	10	
20	27	26-29	11	
21	36	27-36	14 miscarriage	
22	28	28	15 miscarriage	
23	27	27-30	12 miscarriage	
24	30	29	12	279
25	34	28	10	272
26	30	27-30	11	266
27	38	28	11 miscarriage	
28	27	25-27	10-12	
29	29	28	12	274
30	24	27-30	11	
31	28	26-27	10	269
32	34	28	11	
33	30	24-26	9	273
34	21	30	14	273
35	34	24-26	8	224 twins
36	27	30-31	13-15	
37	34	27-29	11	
38	36	26-27	13	261
39	22	32-34	12	255
40	28	26	11	281
41	37	26-29	13 miscarriage	
42	24	33	12 miscarriage	
43	34	26-28	11	
44	33	25-27	10	282
45	26	30	13	295
46	25	28-29	11	
47	33	30-32	12	
48	38	24-27	11	274
49	28	26-27	11	
50	24	26-30	10-13 miscarriage	
51	24	30-42	16-19	
52	34	24-28	10	268
53	25	30	14	
54	40	28-30	12	282
55	28	28-33	11-13	
56	26	33-35	15	265
57	35	24-27	10	266
58	28	25-31	11	267
59	31	28-30	11	273
60	37	25-29	10	268
61	30	30-31	14 mole	
62	29	26-27	10	272
63	31	26-27	10 ectopic	
64	28	30-31	13-15	
65	24	33	12	272
66	32	26-27	10	267

cycles of 26 to 28 days. One patient with a cycle of 24 to 26 days responded on the ninth and one on the eighth day; and two patients with habitual cycles of 24 days terminated as failures.

Temperature Graphs and Endometrial Biopsies

In 1940, following a visit to Zuck's clinic, the writer experimented with temperature graphs as a supplementary measure for revealing the favorable time for artificial insemination. The procedure was found impracticable and was abandoned, except in occasional obscure cases, for the following reasons:

a. Some patients submitted carelessly arranged lists of dates and temperatures which they expected the office to chart and interpret.
b. Many graphs were equivocal in type or vital notations were modified or omitted because of minor illness, travel, or other complications.
c. Typical graphs varied from cycle to cycle in the same patient and the triangular appointment at the office was necessarily made some days before the contemporary graph could be known.

Three patients conceived while experimental graphs were being compiled and, although the material is meager, it was noted that insemination coincided with the day of lowest temperature in two, and was done the following morning in one patient whose previous graphs were atypical. Several articles relative to basal temperatures have been published since 1945, notably that of Tompkins. A correlated study of basal temperatures and endometrial biopsies by Buxton will appear later.

An endometrial biopsy has not been regarded as an essential step in qualifying the wife for a trial of semi-adoption. The writer has long held that evidence of follicular evolution in the ovary gives no assurance that the ovum is intrinsically fecund or that normal implantation of the ovum will be effected. This clinical opinion was based upon many years' experience, during which correlated diagnostic studies of both partners were conducted routinely by the writer. The clinical data supporting this inference will not be detailed again because direct confirmation has been submitted recently by the unique and instructive investigations of Hertig, who assembled, over a period of years, twenty-four uteri in which implantation of the ovum had just occurred. By means of sections through ovum and endometrium he demonstrated ten instances in which an abnormal ovum was associated with a normal secretory endometrium. In four cases, the attachment was so precarious that sloughing and degeneration could be anticipated before menstruation was due. Furthermore, in studying the far more numerous cases of conventional sterility, the writer has found that premenstrual biopsies and curettings from normally menstruating women have been reported, with rare exception, as normally secretory in type. Highly irregular or scanty periods are rarely encountered in the relatively small group of patients seeking semi-adoption because a poor prognosis is anticipated by them.

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SOME PSYCHIC ASPECTS OF DYSMENORRHEA AND NAUSEA AND VOMITING OF PREGNANCY

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THERE have been many reasons given for dysmenorrhea, and as many for nausea and vomiting of pregnancy. Many forms of therapy have been tried for each. Obviously, any disease or symptom complex for which so many forms of treatment are advocated leads to one of three conclusions: first, there are many causes and thus no cure-all; second, the correct cause has not been found, therefore no correct treatment; or third, the basis is psychic. The treatment of the symptoms is still a very urgent problem for the doctor and to the patient, but of all the methods in use today none have proved entirely successful, even though some patients have obtained relief from some of the methods. Was it, however, the particular method or would any one of the many of them have done the same thing?

The cause of dysmenorrhea is unknown, but many theories have been advanced. Among the latter we find cervical stenosis, myometrial insufficiency, mucosal faults, vascular faults, ovarian causes, thyroid causes, anterior hypophyseal causes, allergic phenomena, uterine displacements, psychic and nervous factors. Many of the characteristics of the symptom have led eminent workers to advance a psychogenic basis as the cause.

The symptom complex of nausea and vomiting of pregnancy, like dysmenorrhea, is of unknown etiology, although many theories have been advanced, among them the neurogenic and the psychogenic. Again, as with dysmenorrhea, many therapies have been tried, ranging all the way from sterile hypodermics with a dull needle to hypnosis, forced hydration, and proctoclysis with the patient's own urine, but no one form of treatment has been uniformly successful.

Noting all the emphasis placed on the psychic factors in both dysmenorrhea and also nausea and vomiting of pregnancy, I wondered if the severity of these two symptom complexes ran a parallel course, which might be suggested by the work of Smith and Smith,[1] since they place the two on a common etiologic basis. With this in mind, I interviewed every patient admitted to the obstetric wards of Watts Hospital during the period Jan. 15, 1946, to May 15, 1947, and questioned her as to the severity of her dysmenorrhea and also her nausea and vomiting.

Dysmenorrhea was placed in four groups with the following as the basis for the classification:

1. *No dysmenorrhea*—patient was not aware of menstruation, except for the flow.
2. *Mild dysmenorrhea*—patient had abdominal discomfort, but not severe enough to require any analgesic.
3. *Moderate dysmenorrhea*—patient usually took an analgesic, although sometimes it was only an aspirin.

4. *Severe dysmenorrhea*—patient had severe enough abdominal pain to require her to lose time from work, lose time from her household duties, or require her to go to bed.

Nausea and vomiting of pregnancy was likewise placed in four groups:

1. No nausea nor vomiting—this meant that the patient did not even have morning nausea once.
2. Mild nausea or vomiting—patient had nausea or vomiting which did not persist beyond the first three months.
3. Moderate nausea or vomiting—patient had nausea or vomiting for the entire pregnancy, but not severe enough to require treatment or hospitalization.
4. Severe nausea or vomiting—patient had nausea or vomiting severe enough to require active therapy by injection of vitamins or hospitalization.

No cases of toxemia were included in this series; that is, true toxemia with elevated blood pressure, edema, and albuminuria.

Any classification for gradation of either of the symptom complexes is difficult and probably inadequate because of the difference in pain threshold of different patients, but I tried to minimize this by careful questioning, and, according to Miller,[2] a patient has pain if she thinks she does.

As will be seen from the tables, using the four stages for each of the two symptom complexes, there are sixteen possible combinations.

TABLE I

GRAVIDA	GROUPS 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	TOTAL
i	57	36	4	0	33	164	6	3	21	67	14	4	10	21	7	4	451
ii	61	41	4	2	23	99	8	1	6	29	13	5	0	6	0	4	302
iii	20	18	1	0	9	38	6	0	2	11	8	1	1	3	1	2	121
iv	17	11	1	0	1	16	1	0	1	8	2	0	0	0	0	2	60
v	7	3	2	0	4	11	0	1	0	1	1	1	0	0	0	1	32
vi	5	1	0	0	0	6	1	0	0	4	0	1	1	0	0	0	19
vii	1	1	0	0	0	4	1	0	0	1	1	0	0	0	0	1	10
viii	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	2
ix	1	2	0	0	0	1	0	0	0	0	1	0	0	0	0	0	5
x	0	0	0	0	0	4	0	0	0	1	1	0	0	0	0	0	6
Total	169	113	12	2	70	344	23	5	30	122	42	12	12	30	8	14	1008

Group 1 No dysmenorrhea and no nausea nor vomiting.
Group 2 No dysmenorrhea and mild nausea or vomiting.
Group 3 No dysmenorrhea and moderate nausea or vomiting.
Group 4 No dysmenorrhea and severe nausea or vomiting.
Group 5 Mild dysmenorrhea and no nausea nor vomiting.
Group 6 Mild dysmenorrhea and mild nausea or vomiting.
Group 7 Mild dysmenorrhea and moderate nausea or vomiting.
Group 8 Mild dysmenorrhea and severe nausea or vomiting.
Group 9 Moderate dysmenorrhea and no nausea or vomiting.
Group 10 Moderate dysmenorrhea and mild nausea or vomiting.
Group 11 Moderate dysmenorrhea and moderate nausea or vomiting.
Group 12 Moderate dysmenorrhea and severe nausea or vomiting.
Group 13 Severe dysmenorrhea and no nausea or vomiting.
Group 14 Severe dysmenorrhea and mild nausea or vomiting.
Group 15 Severe dysmenorrhea and moderate nausea or vomiting.
Group 16 Severe dysmenorrhea and severe nausea or vomiting.

Of the total of 1,008 patients, there were 451 primigravidas (44 per cent) and 557 (56 per cent) multigravidas. Of the multigravidas, the largest group was the gravidas ii and iii, these comprising 423 cases (76 per cent) of the multigravidas or 41 per cent of the total. The cases were broken down into

three groups because it was felt that psychologically the primigravidas were different from the others. It was also felt that the gravidas ii and iii were different from those above gravida iii, the distinction being that in most instances the gravida i planned on the first baby, the gravidas ii and iii wanted the baby, and beyond gravida iii, in most cases, the woman didn't know what to do about keeping from having more children or didn't do it.

Those groups containing the largest number of cases were:

1. Mild dysmenorrhea and mild nausea and vomiting—344 cases (34.1 per cent)
2. No dysmenorrhea and no nausea nor vomiting—169 cases (16.7 per cent)
3. Moderate dysmenorrhea and mild nausea and vomiting—122 cases (12.1 per cent)
4. No dysmenorrhea and mild nausea or vomiting—113 cases (11.2 per cent)
5. Mild dysmenorrhea and no nausea nor vomiting—70 cases (6.9 per cent)
6. Moderate dysmenorrhea and moderate nausea or vomiting—42 cases (4.1 per cent)

The four groups that were considered similar were:

1. No dysmenorrhea and no nausea nor vomiting—169 cases (16.7 per cent)
2. Mild dysmenorrhea and mild nausea or vomiting—344 cases (34.1 per cent)
3. Moderate dysmenorrhea and moderate nausea or vomiting—42 cases (4.1 per cent)
4. Severe dysmenorrhea and severe nausea or vomiting—14 cases (1.4 per cent)

If one adds the cases contained in the above four groups we will find that, of the total of 1008 cases, there were 569, or 56.4 per cent, that had absolutely parallel symptoms. If we add to that total the group that had moderate dysmenorrhea and mild nausea or vomiting, 112 cases, for in a great many instances only an aspirin was used to relieve the pain, we obtain a total of 691 cases, or 68.5 per cent of the total, which had parallel courses.

Some of the other groups should be noted. There were only two cases of severe nausea and vomiting in those who had no dysmenorrhea. It will also be noted that there were only five cases of mild dysmenorrhea who had severe nausea or vomiting.

A total of 296 cases had no dysmenorrhea (29.6 per cent). There were 442 cases (43.8 per cent) of mild dysmenorrhea, 206 cases (20.4 per cent) of moderate dysmenorrhea, and 64 cases (6.3 per cent) of severe dysmenorrhea.

There was no nausea nor vomiting in 281 cases (27.8 per cent), mild in 609 cases (60.4 per cent), moderate in only 85 cases (8.4 per cent) and 33 cases (3.2 per cent) had severe nausea or vomiting. Thus there were 70.5 per cent of all the women in the series who had dysmenorrhea of some degree and 72.1 per cent with nausea or vomiting during pregnancy.

It might be contended that, since there were only 56.4 per cent of the cases that had exactly parallel courses, that figure might be obtained on the basis of chance alone. The total number of cases in each group are not in parentheses while the number that would be expected in that group on the basis of chance alone are included in the parenthesis. It will be seen from a comparison of the figures that in only a few instances are they very close together, as might be expected if the distribution of my cases took place on the chance basis. In a table of the type I have set up, the distribution should run from the upper left-hand corner to the lower right-hand corner. Let us compare the figures in the

parentheses with the total number of actual cases in each instance, for the total number of cases for the other groups are closely parallel:

1. No dysmenorrhea and no nausea or vomiting—a total of 169 cases, while on the basis of chance alone there should be only 82.
2. Mild nausea or vomiting and mild dysmenorrhea—a total of 344 cases, while on the basis of chance alone there should be 266.
3. Moderate dysmenorrhea and moderate nausea or vomiting—a total of 42 cases, while chance provides for only 17.
4. Severe dysmenorrhea and severe nausea or vomiting—a total of 14 cases, where there should have been only 2 on a chance basis.

Adding the total number of actual cases, we have 569, while by chance alone we should have had only 367, a difference of 202 cases. This is 55 per cent more than would be expected on the basis of chance alone. In the primigravidas, this difference amounted to 44 per cent, in the gravidas ii and iii to 57 per cent, and in the gravidas iv and above to 88 per cent. Thus the gravidas ii and iii came nearer to the standard for the group as a whole, while the gravidas iv and above showed the most marked difference. The latter might possibly be accounted for on the basis of a greater number of repeated insults.

TABLE II. ALL CASES

	DYSMENORRHEA								
	NONE		MILD		MODERATE		SEVERE		TOTAL
No nausea or vomiting	169	(82)	70	(123)	30	(57)	12	(18)	281
Mild nausea or vomiting	113	(178)	344	(266)	122	(124)	30	(38)	609
Moderate nausea or vomiting	12	(25)	23	(37)	42	(17)	8	(5)	85
Severe nausea or vomiting	2	(9)	5	(14)	12	(6)	14	(2)	33
Total	296		442		206		64		1008

TABLE III. PRIMIGRAVIDAS

	DYSMENORRHEA								
	NONE		MILD		MODERATE		SEVERE		TOTAL
No nausea or vomiting	57	(26)	33	(55)	21	(28)	10	(11)	121
Mild nausea or vomiting	36	(62)	164	(131)	67	(67)	21	(26)	288
Moderate nausea or vomiting	4	(7)	6	(14)	14	(7)	7	(3)	31
Severe nausea or vomiting	0	(2)	3	(5)	4	(2)	4	(1)	11
Total	97		206		106		42		451

TABLE IV. GRAVIDAS II AND III

	DYSMENORRHEA								
	NONE		MILD		MODERATE		SEVERE		TOTAL
No nausea or vomiting	81	(42)	32	(53)	8	(21)	1	(4)	122
Mild nausea or vomiting	59	(84)	137	(106)	40	(43)	9	(9)	245
Moderate nausea or vomiting	5	(14)	14	(17)	21	(7)	1	(1)	41
Severe nausea or vomiting	2	(5)	1	(6)	6	(3)	6	(1)	15
Total	147		184		75		17		423

TABLE V. GRAVIDAS IV AND OVER

	DYSMENORRHEA								
	NONE		MILD		MODERATE		SEVERE		TOTAL
No nausea or vomiting	31	(14)	5	(14)	1	(7)	1	(1)	38
Mild nausea or vomiting	18	(29)	43	(29)	15	(14)	0	(2)	76
Moderate nausea or vomiting	3	(5)	3	(5)	7	(2)	0	(0.4)	13
Severe nausea or vomiting	0	(2)	1	(2)	2	(1)	4	(0.2)	7
Total	52		52		25		5		134

In conclusion, my correlation shows that there is some common factor between dysmenorrhea and nausea and vomiting which could be psychogenic and the statistics cause one to have grave suspicion that such may be the case, since there is no obvious anatomic or physiologic relationship known.

Summary

1. One thousand and eight patients were interviewed with regard to dysmenorrhea and nausea and vomiting of pregnancy.
2. There was no dysmenorrhea in 296 cases (29.6 per cent).
3. There was no nausea nor vomiting in 281 cases (27.8 per cent).
4. There were 569 cases (56.4 per cent) that had absolutely parallel symptoms, and to this might be added another 122 cases, making the total 691 cases (68.5 per cent).
5. A review of the number of cases obtained in each group in comparison with the number that would be expected on a chance basis alone leads one to the conclusion that there is some common factor between dysmenorrhea and nausea and vomiting of pregnancy that could very well be psychogenic, since there is no obvious common anatomic nor physiologic relationship known.

The author expresses his appreciation to Dr. Eleanor B. Easley for her helpful criticisms and suggestions during the preparation of this article.

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BACTERIAL FLORA IN INFANTS ENCOUNTERED AT TIME OF DELIVERY*

A Study of One Hundred Cultures from the Eyelids

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THE obstetrician is concerned with the bacterial flora contaminating the operative field at the time of the delivery of an infant. Both he and the pediatrician are interested in the incidence and types of organisms from the mother which might cause ophthalmia neonatorum in the newborn infant. As a method of demonstrating this bacterial flora, one hundred cultures were taken from the eyelids of newborn infants immediately after birth, before the umbilical cord was cut.

Mothers of Infants Studied

Nearly all of the mothers were charity patients. Seventy-nine per cent belonged to the Negro race. They were unselected, except that no patient was included who had not been completely draped and prepared for delivery in the usual manner.

In order to evaluate the incidence of venereal disease in this group, the Kahn test of the mother at the time of the first prenatal visit was noted, and the mother was questioned at the time of delivery regarding a vaginal discharge occurring prior to the present pregnancy and whether or not she had received treatment for it. She was also questioned about having received therapy for syphilis.

The Kahn test was known in 77 patients and was positive in 5 (6.5 per cent). Twelve (14.4 per cent) out of 83 patients (unknown in 17) had received therapy for syphilis. Thirty-eight (40.4 per cent) out of 94 patients (unreliable history in 6) gave a history of a vaginal discharge, and 13 (13.6 per cent) had received treatment for it.

Eighty-nine per cent of the patients had not had a vaginal examination during labor; 9 per cent had had one, and 2 per cent had had two vaginal examinations. The membranes had been ruptured less than twelve hours in 83 per cent.

Collection of Specimens for Culture

The cultures were taken before the umbilical cord of the infant was cut, to rule out any possible contamination other than from the mother. A sterile swab was wiped across the eyelids along the line of approximation of the eyelid margins. The eyes were closed at the time. This was done on

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each eye and the swabs put in a tube of nutrient broth. Cultures taken at night were kept in a refrigerator for plating the following morning.

Baceriologic Procedures

The two swabs were streaked across the surfaces of two plates containing McLeod's medium for isolation of the gonococcus, two blood agar plates, and one eosin methylene-blue agar plate. The broth in the specimen tube was then distributed in approximately equal portions into two tubes of blood tryptose broth.

One tube of blood tryptose broth, one blood agar plate, and the eosin methylene-blue agar plate were incubated at 37.5°C. The other tube of blood tryptose broth and the second blood agar plate were sealed in an earthenware jar, using the Varney[1] method for detecting anaerobic organisms and incubated at 37.5° C. The two plates of McLeod's medium were sealed under 10 per cent carbon dioxide tension, using the method of Wadsworth,[2] and incubated at 37.5° C. The container was a screw top, five-pound coffee jar which possessed an inner top with a rubber ring to aid in sealing.

At the end of twenty-four hours, the two blood agar plates, the eosin methylene-blue agar plate, and the two culture tubes of blood tryptose broth were examined. If negative, they were examined again at the end of forty-eight hours. At the end of forty-eight hours, the two plates of McLeod's medium were carefully examined for colonies of Neisseriae. All plates which were negative after forty-eight hours of incubation were discarded. All broths which were negative after forty-eight hours of incubation were retained and re-examined five days after the specimen was collected. At the end of this period, if the broths were still negative, the culture was considered negative. If positive, the broths were streaked on plates and identification of the organism or organisms made.

Organisms were studied as to microscopic appearance and colony formation. Staphylococci were classified as to their pigment formation, and their capacity for hemolyzing blood and coagulating plasma. The bile solubility test was used to differentiate between streptococcus viridans and the pneumococcus. Gram-negative rods were grouped as to motility, pigment formation, their ability to form spores, and action on carbohydrates. Gram-positive rods which gave the microscopic appearance of Corynebacteria were inoculated to carbohydrate broths to differentiate *C. xerose, C. hoffmannii,* and *C. diphtheriae.* All yeasts were incubated on carbohydrate broths for identification. When colonies suggestive of Neisseriae were found on the plates containing McLeod's medium, they were tested for the "oxidase reaction." Colonies giving a positive reaction were transferred to tubes of dextrose, maltose, and saccharose media which were incubated for forty-eight hours under 10 per cent carbon dioxide tension to differentiate the varieties of Neisseriae.

Results

Ninety-six per cent of the cultures were positive. Thirty-eight per cent were positive for one organism; 46 per cent for two organisms; 11 per cent for three organisms; and 1 per cent for four organisms. A total of 167 organisms were isolated in the 96 positive cultures (Table I).

Staphylococci, Escherichia coli, and Streptococcus accounted for approximately three-fourths (76.5 per cent) of the organisms encountered. Twenty-six varieties of organisms were found.

TABLE I. TYPE AND INCIDENCE OF ORGANISMS FOUND IN POSITIVE CULTURES FROM EYELIDS OF NEWBORNS IMMEDIATELY AFTER BIRTH

ORGANISM	INCIDENCE		PER CENT OF TOTAL
Staphylococcus aureus			
*hemolytic, plasma, coagulase negative	10		
*hemolytic, facultative aerobe, plasma coagulase negative	1		
nonhemolytic, plasma, coagulase negative	9		
nonhemolytic, facultative anaerobe, plasma coagulase negative	1	50	29.9
Staphylococcus albus			
hemolytic, plasma, coagulase negative	9		
nonhemolytic, plasma, coagulase negative	19		
Staphylococcus, unclassified	1		
Escherichia coli		40	24.0
Streptococcus			
alpha hemolytic	1		
alpha-hemolytic, anaerobic	7		
*beta-hemolytic	2		
*beta-hemolytic, anaerobic	6		
*beta-hemolytic, facultative anaerobe	4	36	21.6
nonhemolytic	2		
nonhemolytic, facultative aerobe	3		
nonhemolytic, anaerobic	8		
nonhemolytic, facultative anaerobe	3		
Gram-positive sporulating bacillus, unclassified		11	6.6
**Monilia albicans*		8	4.8
**Bacterium aerogenes*		5	3.0
Diphtheroid, unclassified		5	3.0
Gram-negative sporulating bacillus, anaerobic, unclassified		3	1.8
Corynebacterium xerose		2	1.2
Corynebacterium hoffmannii		1	1.6
*Gram-negative diplococcus, positive oxidase, atypical fermentation reactions for gonococcus		1	.6
Member of Colon-aerogenes group		1	.6
Gram-negative nonsporulating bacillus, unclassified		1	.6
Gram-negative nonsporulating gas-producing bacillus, unclassified		1	.6
Gram-positive coccus, unclassified		1	.6
Gram-positive coccus, anaerobic, unclassified		1	.6
Total		167	

*Potential pathogens

Of the total organisms isolated, 15.0 per cent were anaerobes and 4.8 per cent were facultative anaerobes making a total of 19.8 per cent showing culture preference for anaerobic conditions (Table II). Facultative aerobes comprised 2.4 per cent of the total.

TABLE II. INCIDENCE OF AEROBIC AND ANAEROBIC ORGANISMS

AEROBE				ANAEROBE			
OBLIGATE		FACULTATIVE		OBLIGATE		FACULTATIVE	
NUMBER	PER CENT OF TOTAL*	NUMBER	PER CENT OF TOTAL	NUMBER	PER CENT OF TOTAL	NUMBER	PER CENT OF TOTAL
130	77.8	4	2.4	25	15.0	8	4.8

*Total of 167 organisms isolated in 100 cultures from surface of eyelids immediately after birth.

Table III groups the staphylococci according to hemolysis; 59.2 per cent were nonhemolytic and 40.8 per cent were hemolytic. No staphylococci were found with the ability to coagulate plasma.

TABLE III. INCIDENCE OF HEMOLYSIS AMONG STAPHYLOCOCCI ISOLATED

NONHEMOLYTIC		HEMOLYTIC	
NUMBER	PER CENT OF TOTAL*	NUMBER	PER CENT OF TOTAL
29	59.2	20	40.8

*Total of 49 staphylococci (unclassified staphylococcus not included).

Of the total of 36 streptococci identified, 44.4 per cent were nonhemolytic and 55.6 per cent were hemolytic. Alpha- and beta-hemolytic streptococci comprised, respectively, 22.2 per cent and 33.3 per cent of the total (Table IV).

Only one organism encountered belonged to the Neisserian group and this organism did not give a typical fermentation reaction for the gonococcus.

TABLE IV. INCIDENCE OF TYPES OF STREPTOCOCCI ISOLATED

NONHEMOLYTIC		ALPHA-HEMOLYTIC		BETA-HEMOLYTIC	
NUMBER	PER CENT OF TOTAL*	NUMBER	PER CENT OF TOTAL	NUMBER	PER CENT OF TOTAL
16	44.4	8	22.2	12	33.3

*Total of 36 streptococci.

Comment

In this series, cultures were taken from the external surface of the eyelids rather than from the conjunctivas. This method was used to demonstrate both the bacterial flora present during parturition and as many varieties of organisms as possible which might contaminate the eyes of the newborn before, during, or after delivery.

It is probable that the incidence of *E. coli* is made high by contamination from the perineal region.

These results demonstrate how the birth canal and, probably to a lesser extent, the perineal region serve as a source of contamination for the eyes of the newborn infant.

If one selects each potential pathogenic organism (hemolytic *staphylococcus aureus, beta-hemolytic streptococcus, Monilia albicans, Bacterium aerogenes,* gram-negative diplococcus, and members of Colon-aerogenes group) from those listed in Table I, a total of 38 (22.4 per cent) is found. This percentage probably represents a conservative estimate of those which would be capable, under proper conditions, of causing ophthalmia neonatorum.

On the other hand, Sorsby and associates[3, 4] reported in 1942 and 1944 the organisms detected by smear and culture in 591 cases of ophthalmia neonatorum. Of the organisms isolated in this study, their tables included *staphylococcus albus* (without subdivision), *staphylococcus aureus* (without subdivision), *alpha-hemolytic streptococcus,* diphtheroid, *corynebacterium xerose, corynebacterium Hoffmannii,* and gram-positive cocci. Thus, it is likely that, of the organisms isolated in this study, the percentage capable of causing ophthalmia neonatorum is somewhat above 22.8.

A comparison may be made between these results and those of Whitacre and associates[5] obtained from uterine cultures taken during the first five days post partum. The two series may be considered comparable in that each

was from the same maternity service. The most frequently encountered organisms in each series were streptococci, staphylococci, and *Escherichia coli.* However, the order of frequency is different as follows (parentheses refer to Whitacre's series): Staphylococci, 29.9 per cent (17 per cent), *E. coli,* 24.0 per cent (14 per cent), and streptococci 21.6 per cent (54 per cent). The high frequency of streptococci in this comparable series would indicate that, of the three organisms, streptococcus most easily invades the uterus from the birth canal.

In view of the incidence of venereal disease in the mothers of the infants studied, the isolation of only one organism belonging to the Neisserian group was surprising. In the previously mentioned series of Whitacre and associates, 3 per cent of the organisms isolated were of the Neisserian group. Dilution of the contaminating secretion with amniotic fluid or the presence of liquid soap used for lubrication during delivery may possibly interfere with the isolation of the gonococcus from the specimens collected.

Summary

One hundred cultures were taken from the external surface of the eyelids of newborn infants immediately after birth and before the cord was cut. Ninety-six per cent of the cultures were positive, and from one to four organisms were isolated in each positive culture. A total of 167 organisms were identified of which *Staphylococci, E. coli,* and *Streptococci* were predominant.

Appreciation is expressed to Frank E. Whitacre, M.D., Professor of Obstetrics and Gynecology, and Anna Dean Dulaney, Ph.D., Assistant Professor of Bacteriology, for assistance in this work.

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DECIDUAL BLEEDING IN PREGNANCY*

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BLEEDING during the first four to five months of pregnancy frequently presents a puzzling diagnostic problem. If we eliminate threatened, inevitable, and incomplete abortions, tubal pregnancy, premature separation of the placenta, placenta previa, and cervical pathology, there still remains a group of patients who have vaginal bleeding but who seem also to have normally progressive uterine enlargement. The tentative diagnoses are usually those of threatened abortion, premature separation or low implantation of the placenta and, occasionally, placenta previa. Close observation and inspection of the placenta and fetal membranes do not confirm these premises. We have, however, almost invariably found gross evidence of an unhealthy decidua in these patients. The pathology seems to consist in degeneration with leucocytic infiltration of portions of the decidua vera, and, in most instances, a placque or placques of such decidua are to be found intimately adherent to the maternal surface of the membranes. A rather careful search of the various texts and the literature offers little or no illumination.

During the last year we have followed thirteen such pregnancies to their termination. We attempt to summarize the clinical and laboratory findings, the end results of these pregnancies, and the therapy instituted.

Bleeding in varying amounts from moderately profuse to slight was present in all these patients. Cramps and bleeding were present in four instances, and when present together justified a poor prognosis for continuation of the pregnancy. The duration of pregnancy after the onset of cramps was four weeks in two instances and six weeks in two other cases. The following case histories are illustrative:

Case 1.—C. D., No. 73141, 31 years of age, gravida iv, last menstrual period, Dec. 15, 1946, estimated date of confinement, Sept. 22, 1947. Previous medical history, negative, Rh positive, serology negative. Menstrual history, began at 15 years of age, every 28 days for five days. Obstetrical history: 1942, ten weeks, spontaneous abortion. 1943, term, labor, eighteen hours, spontaneous delivery 5½ pounds, stillborn. 1946, six months, premature separation of placenta, stillborn.

This patient was first seen April 7, 1947 (3½ months). She was admitted to the hospital June 30, 1947 (6 months), because of bright red bleeding, accompanied by uterine contractions at frequent intervals with poor relaxation between. The fetal heart sounds were normal. She was given sedation, bed rest, and Lipo-Lutin, 10 mg. three times a day. The bleeding diminished and stopped after three days. Patient was given a transfusion of 500 c.c. citrated blood because of a hemoglobin of 56 per cent. She was then discharged and advised to rest at home. Our tentative diagnosis was that of possible mild separation of placenta.

The patient was readmitted July 22, 1947 (7 months), because of slight vaginal bleeding and was found to be in definite labor. The fetal heart sounds were normal. She delivered

*Read before the Pittsburgh Obstetrical and Gynecological Society, Oct. 6, 1947.

spontaneously after an eight-hour labor. A living female child, weight 1,475 Gm., survived. The placenta showed large placques of degenerating decidua over most of the maternal surface of the membranes. There was no evidence of marginal placenta previa or of premature separation of placenta.

CASE 2.—A. B., No. 78584, 33 years of age, gravida i, last menstrual period, Sept. 5, 1946, estimated date of confinement, June 12, 1947, previous medical history, negative, basal metabolism plus 13 per cent, Kahn negative, Rh positive. Menstrual history: Periods began at 16 years of age and occurred intermittently and profusely for one year, after which they came every 28-30 days, were of five-day duration and moderate in amount.

The patient was first seen Oct. 25, 1946, at five weeks gestation. She gave a history of having had a tan discharge from October 5 to 12, with recurrence October 23. Examination revealed no bleeding. There was a fibroid about 5 cm. in diameter in the left cornual region. She was given Premarin tablets, one every third day, and Pranone, 20 mg. daily until the end of the fourth month. She was seen again Nov. 19, 1946, because of a history of slight bleeding one day in duration on four occasions since last visit. The fetal heart sounds were heard at four months.

Labor began May 17, 1947 (8 months), was of sixteen hours' duration and was terminated by low forceps delivery. A living female child 44 cm. long, weighing five pounds twelve ounces, survived.

A placque of degenerating decidua 8 by 9 by 3 cm. was adherent to the maternal surface of the membranes near the edge of placenta. The placenta and membranes were otherwise normal.

CASE 3.—R. O., No. 75654, 30 years of age, gravida i, last menstrual period, Feb. 19, 1946, estimated date of confinement, Nov. 26, 1946, previous medical history, negative, serology negative, Rh positive. Menstrual history: Periods began at 13 years of age, occurred every 28 days for four days. The probable beginning of pregnancy was March 4, 1946. Bright red bleeding was noticed from April 17 to April 27.

She was first seen May 6, 1946, still having a slight tan discharge, and was given Premarin tablets, one every third day, and Pranone 20 mg. daily for three weeks. The bleeding ceased May 27 and did not recur. The fetal heart sounds were heard June 25, 1946 (3¾ months).

Labor began Nov. 10, 1946 (8½ months). The baby, which survived, weighed four pounds and fourteen ounces and the placenta 435 Gm. Several placques of degenerated decidua were present on the membranes.

CASE 4.—G. B., No. 74185, 30 years of age, gravida i, last menstrual period, March 14, 1946, estimated date of confinement, Dec. 21, 1946, previous medical history, right oophorectomy and appendectomy at 17 years of age (cystic ovary). Basal rate normal, Kahn negative, Rh positive. Menstrual history: Onset of menses at 12-13 years of age, every 28 days for five days with severe dysmenorrhea the first two days.

The patient was first seen Aug. 8, 1946. She gave a history of painless bleeding (bright red) June 9, 19, 29, and July 11, and had been having a continuous brown discharge since July 21. In the last few days before admission she had several gushes of bright red blood, less than during her menses. There were no cramps but uterine contractions were perceptible to the patient. From August 8 to August 30, there were bleeding and cramps intermittently and the uterus was quite irritable. The fetal heart sounds were normal. The patient passed a small mass of brownish tissue August 20. It was reported to be "decidual tissue (degenerated) with chronic inflammatory reaction."

Pregnancy terminated in spontaneous abortion August 30 (5½ months). The placenta, membranes, cord, and a mass of pale tan fleshy tissue were passed en masse.

The placenta measured 9 by 8.5 by 3 cm. The maternal surface was bloodstained and fleshy, with no areas of attached clot. The cotyledons were well demarcated and intact, and the fetal surface was pale and shiny. The membranes were thick and to the maternal surface were adherent placques of tan, fleshy tissue. The mass of tissue accompanying the placenta

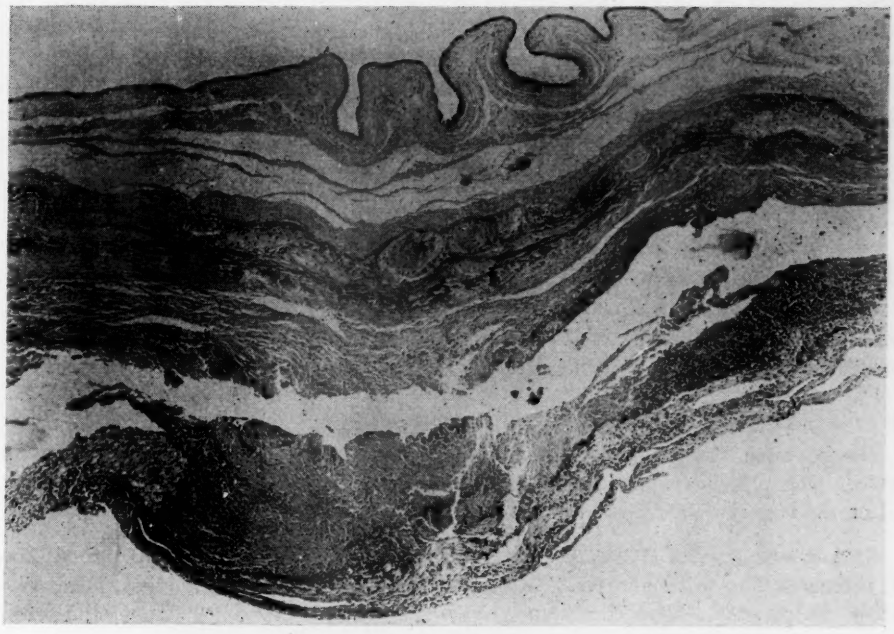

Fig. 1.—Cross section of amnion, chorion and degenerated decidual placque.

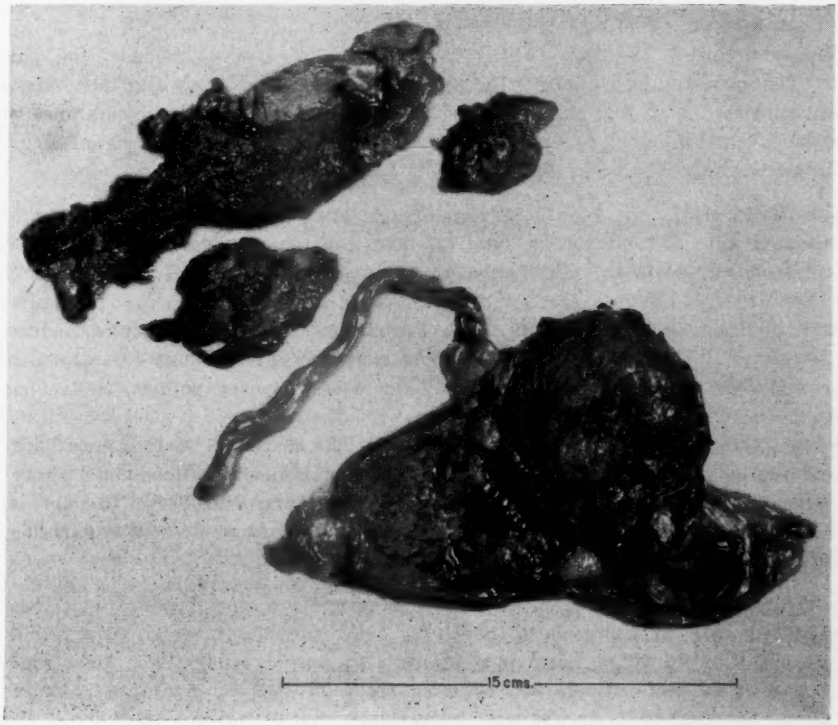

Fig. 2.—Placenta with degenerated decidua on maternal surface of membranes and two large placques of similar decidua.

measured 1 to 1.5 cm. in thickness and 13 cm. in length. Microscopic examination revealed placental villi and showed also varying degrees of organization of villi. A considerable amount of decidual tissue exhibiting acute and chronic inflammation was attached to the maternal surface of the membranes. The large mass of tissue consisted of "degenerating decidua with inflammatory reaction."

The fetus measured in length 32 cm. (6 months), weighed 495 Gm., was of male sex, and did not survive. Dilatation and evacuation performed Sept. 9, 1946, for continued lochia rubra produced degenerating decidua.

CASE 5.—D. T., 28 years of age, gravida iii, last menstrual period, July 15, 1946, estimated date of confinement, April 22, 1947, previous medical history, negative, Kahn negative, Rh positive. Menstrual history: Periods began at 15 years of age, and occurred every 28 days for four days. Obstetrical history: 1940, term, five pounds, eight ounces. 1944, term, six pounds, thirteen ounces.

Patient was first seen Jan. 22, 1947 (6 months). She gave a history of bleeding for three days in October, treated by bed rest, and of spotting intermittently since.

She delivered March 28, 1947 (8 months). A male baby weighing five pounds six ounces survived. The placenta appeared normal (475 Gm.). Degenerating decidual placques were found on the maternal surface of the membranes.

CASE 6.—C. B., No. 69333, 34 years of age, gravida ii, last menstrual period, March 9, 1946, estimated date of confinement, Dec. 16, 1946, previous medical history, negative, Kahn negative, Rh positive. Menstrual history: Menses began at 15 years of age, and were regular every 28 days for six days. Obstetric history: One previous full term pregnancy, 1945.

Patient was first seen Aug. 1, 1946. She began bleeding May 8, 1946, and was admitted to hospital for nine days because of slight intermittent bleeding which continued throughout June and was moderately profuse for the first two weeks of the latter month. The right ovary was enlarged to five times normal size. There was a small adenoma of the thyroid. Proloid, 1 grain (65 mg.) daily, was ordered.

Delivery occurred Dec. 12, 1946. The baby weighed seven pounds, ten ounces and survived. The placenta measured 15 by 15 by 2.5 cm. Its maternal surface was pale, red and fleshy, and the cotyledons were well demarcated and normal. The membranes were thin and translucent and applied to the maternal surface was a large placque of degenerating decidua approximately 7.5 cm. in diameter.

CASE 7.—P. McK., No. 74551, 20 years of age, gravida i, last menstrual period, Nov. 25, 1945, estimated date of confinement, Sept. 2, 1946, previous medical history, negative, Kahn negative. Menstrual history: Menses began at 14 years of age and were regular every 28 days for five days.

The patient was first seen May 27, 1946 (5 months), and gave a history of moderate bleeding for two days in April, recurring two weeks later in slight amount for several days.

She delivered September 2, 1946, The baby weighed seven pounds, twelve ounces and survived.

The placenta measured 17 by 15 by 3 cm. The maternal surface was dark-red and meaty and the cotyledons were well marked. The membranes were complete, shiny, and on the maternal surface near the placenta were two flat placques, dark brown in color, measuring 5 and 3 cm. in diameter. Microscopic section of these placques showed organizing and degenerating decidual tissue.

CASE 8.—I. H., No. 72771, 32 years of age, gravida iv, last menstrual period, Dec. 10, 1945, estimated date of confinement, Sept. 12, 1946, previous medical history, mild hyperthyroidism, duration 16 years, basal plus 17 per cent, serology negative. Menstrual history: Menses began at 13 years of age and occurred every 28 days for five days. Obstetrical history: 1940, 6½ months' pregnancy, hemorrhage ante partum, stillborn. 1942, term pregnancy, normal, low forceps delivery, seven pounds, twelve ounces. 1944, term pregnancy, breech extraction, six pounds, twelve ounces.

The patient was first seen March 20, 1946 (3 months). There had been a sudden gush of bright red blood Feb. 25 (2 months), and bleeding had continued intermittently thereafter accompanied by occasional slight cramps.

She was admitted to the hospital May 3, 1946. There was slight bleeding and the uterus was contracting every three minutes. The fetal heart sounds were not heard. A stillborn fetus was aborted spontaneously May 4, 1946 (4½ months).

The placenta showed an unusually thick set of membranes with a heavy layer of dark brown decidua over most of the maternal surface. The placenta itself was normal. Section through the thickened portion of the membranes revealed heavy layers of degenerating decidua.

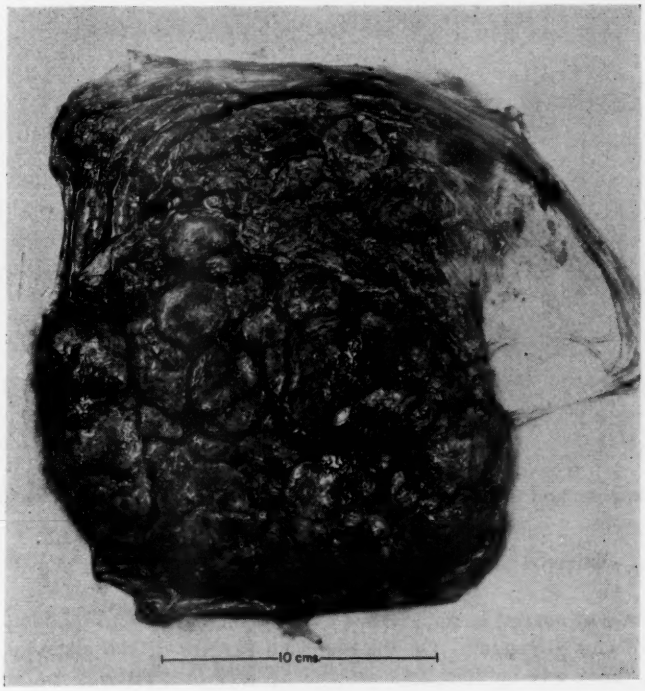

Fig. 3.—Thick layer of degenerated decidua adherent to maternal surface of membranes.

CASE 9.—B. S., No. 76537, 20 years of age, gravida ii, last menstrual period July 20, 1946, estimated date of confinement, May 27, 1947, previous medical history, negative, Kahn negative. Menstrual history: Periods began at 12 years of age, every 28-30 days for five days. Obstetrical history: 1946, 9½ months' pregnancy, breech extraction, six pounds, nine ounces.

The patient gave a history of sudden repeated gushes of blood November 5 to 18 (3 plus months). She was first seen Nov. 19, 1946. December 22 she reported that she had been having intermittent slight dark red discharge. The fetal heart sounds were normal (5 months). There was a small cervical polyp present which was examined and found to be decidual in origin. The patient was admitted to the hospital Jan. 7, 1947, because of increase in bleeding accompanied by slight cramps. The fetal heart sounds were still present (5½ months).

Spontaneous abortion occurred Jan. 8, 1947. The fetus did not survive.

The specimen consisted of a complete placenta, intact membranes and enclosed fetus. The entire maternal surface of the membranes was covered by a thick coat of grayish brown decidua which was moderately adherent and in scattered areas was permeated with blood. Microscopic sections revealed necrotic decidua.

CASE 10.—L. A., No. 26776, 27 years of age, gravida iii, last menstrual period, April 20, 1946, estimated date of confinement, Jan. 27, 1947, previous medical history, negative,

serology negative. Menstrual history: Periods began at 12 years of age, and were every 26 days for five days. Obstetrical history: 1942, term pregnancy, normal delivery, eight pounds, four ounces. 1944, term pregnancy, normal delivery, eight pounds.

She was first seen July 30, 1946, and gave a history of slight to moderate bleeding for ten days, beginning July 13. The fetal heart sounds were heard August 20, 1946 (3¾ months).

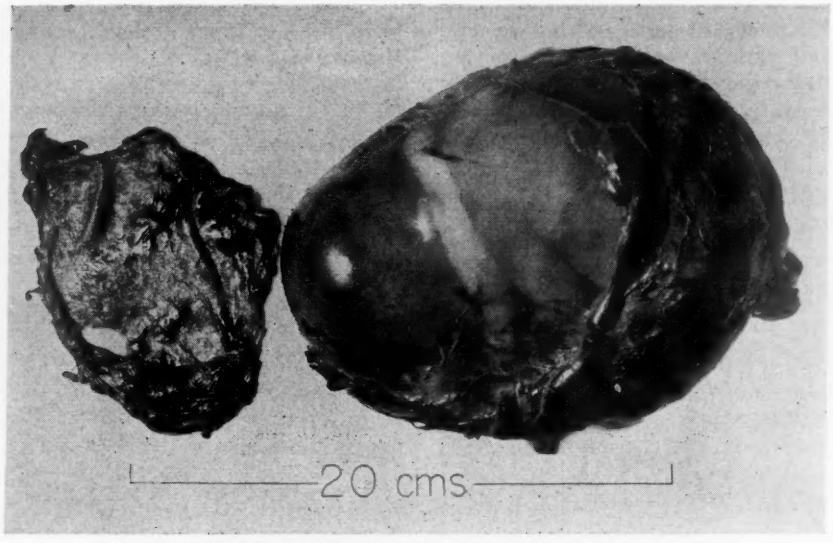

Fig. 4.—Placenta, sac, and enclosed fetus. Membranes entirely covered with thick layer of degenerated decidua.

The patient delivered Jan. 22, 1947. The baby weighed eight pounds, eight ounces and survived.

The placenta was normal in appearance and measured 20 by 18 by 2 cm. The membranes were smooth, pale and glistening. On the maternal surface of the membranes, near the edge of the placenta, there was an irregular placque of soft brownish-red material 7.5 cm. in diameter, resembling decidua. Microscopic sections through this area showed it to consist of degenerating decidua.

CASE 11.—A. A., No. 49599, 25 years of age, gravida v, last menstrual period, Sept. 12, 1946, estimated date of confinement, June 19, 1947, previous medical history, negative, serology negative, Rh positive. Menstrual history: Periods began at 12 years of age, and occurred regularly every 30 days for five days.

Obstetrical history:

1941, 10 months' pregnancy, normal delivery, six pounds,eight,ounces.
1942, 10 months' pregnancy, normal delivery, eight pounds.
1943, 10¼ months' pregnancy, normal delivery, seven pounds, eight ounces. Symptoms of threatened abortion occurred at two months' gestation.
1945, 10 months' pregnancy, normal delivery, six pounds.

She was first seen Dec. 11, 1946 (2¾ months), and later gave a history of having had brown discharge from Dec. 11 to Dec. 31, 1946. The fetal heart sounds were heard Dec. 31, 1946 (3¼ months).

She was delivered June 3, 1947 (8½ months) of a living child. The fetal and maternal surfaces of the placenta were normal. There was a placque of degenerating decidua 3.5 by 2 by 3 cm. on the maternal surface of the membranes. This was confirmed by microscopic examination.

CASE 12.—B. W., No. 79332, 21 years of age, gravida i, last menstrual period December, 1946 (?), estimated date of confinement, September, 1947, previous medical history, negative, serology negative, Rh negative. Menstrual history: Periods began at 16 years of age and occurred every 30 to 60 days for four days.

She was first seen June 30, 1947 (6 months), and gave a history of having had slight bleeding for twelve days at the end of December.

She delivered June 30, 1947. The baby weighed five pounds ten ounces, was 40 cm. in length, and survived (8 months' gestation).

The placenta appeared complete and normal. There was a placque of degenerating decidua on the maternal surface of the membranes measuring 9 by 7 by 2 cm.

CASE 13.—D. S., 26 years of age, gravida ii, last menstrual period, Nov. 21, 1946, estimated date of confinement, Aug. 28, 1947, previous medical history, the Friedman test was positive Jan. 20, 1947. The patient was given vitamin E and thyroid. The basal reading was minus 25 per cent. Menstrual history: Menses began at 16 years of age and were irregular from onset. Obstetrical history: Previous left salpingectomy for tubal pregnancy.

Bleeding began Dec. 23, 1946, and was slight in amount until Feb. 16, 1947. Profuse bleeding began February 16 and patient was admitted to the hospital for observation. She was discharged March 4, 1947, but continued to have slight bleeding until April 26.

Labor began Aug. 18, 1947, and terminated in the birth of a normal male child weighing six pounds five ounces, which survived. There was a large amount (several placques) of homogeneous, necrotic, reddish-tan tissue adherent to maternal surface of membranes. Microscopic examination revealed degenerating decidua with inflammatory infiltration.

The essential data regarding these cases may be tabulated as follows:

Age 20 to 34:
- In 20's—7
- In 30's—6

Menstrual history:
- Abnormal, 3 in 20's, 4 in 30's
- Normal, 4 in 20's, 2 in 30's

Onset of symptoms:
- At 4 to 12 weeks, 11
- From 12 weeks on, 2

Duration of pregnancy:
- 4½ months, 1
- 5 months, 2
- 7 months, 1
- 8 months, 3
- 8½ months, 3
- Term, 3

Initial diagnosis:
- Premature separation of placenta, 2
- Threatened abortion, fibroid uterus, 1
- Threatened abortion, 9
- Low implantation of placenta, 1

Therapy:
- Ambulatory, 1
- Bed rest, 5
- Bed rest and endocrine therapy, 7

Gross fetal survival, 10—77 per cent

Viable fetal survival, 100 per cent
- Primigravida, 5; fetus survived, 4, stillborn, 1
- Multigravida, 8; fetus survived, 6, stillborn, 2

Summary

A series of thirteen patients who exhibited vaginal bleeding during the first four and one-half to five months of pregnancy is presented.

The initial diagnoses included premature separation of the placenta, threatened abortion and fibroid uterus, threatened abortion and low implantation of the placenta.

Seven patients were in the second and six in the third decade of life.

The menstrual history was abnormal in fifty per cent of the patients.

The onset of symptoms began at from four to ten weeks in eleven patients and twelve weeks in two patients.

The bleeding occurred in varying amounts, from slight to moderately profuse in all patients, and was accompanied by cramps and definite uterine contractions in four instances. The onset of the latter symptoms was a poor prognostic sign; the four patients so afflicted aborted in from four to six weeks thereafter.

The pregnancies were of the following duration:

STILLBIRTHS		SURVIVED			
4½ months	5 months	7 months	8 months	8½ months	Term
1	2	1	3	3	3

Ten babies survived, 77 per cent. Viable survival, 100 per cent.

There were five primigravidas and eight multigravidas.

One patient was fully ambulatory without any therapy, five were on bed rest alone, and the remaining seven were kept in bed and given estrogen and progesterone therapy.

The final outcome of the pregnancies seemed to depend on the extent of the decidual degeneration. In no instance was there found evidence of subplacental hematomas or gross placental pathology.

Conclusions

Apparently, early bleeding in pregnancy may result from degenerating decidual tissue. This decidual degeneration has seemed to be largely, if not entirely, confined to the decidua vera.

One of the patients in this series presented an apparent cervical polyp, which, on microscopic examination, was found to consist of degenerated decidua, confirming the findings in three cases reported by Haas.[1]

Normal progression of the pregnancy, with gradual cessation of the bleeding, examination of any tissue passed, and inspection of the placenta and membranes following delivery will make the final diagnosis.

The early elicitation of fetal heart sounds is of diagnostic and prognostic value.

Conservative management of these patients is indicated. The value of endocrine therapy appears to be questionable.

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CHRONIC ULCERATIVE COLITIS AND PREGNANCY

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THERE is a marked paucity of published data concerning pregnancy in women patients suffering from chronic ulcerative colitis. Barnes[1] and Saegesser[2] report a few cases which they interpreted as possible manifestations of toxemia of pregnancy. Bargen[3] described seventeen patients in whom pregnancy was associated with chronic ulcerative colitis in twenty-two instances.

Material

The present communication concerns 34 women and 50 gestations. These patients were part of a group of 362 men and 421 women with chronic ulcerative colitis under our care, constituting 8 per cent of the total number of women. There were 43 full-term deliveries, 3 miscarriages, 2 therapeutic abortions, 1 tubal pregnancy, and 1 induction of labor during the sixth month. Thirty of the patients under consideration were between the ages of 20 and 31 years and 4 were between 31 and 38 years. In eight instances (23 per cent) the manifestations of chronic ulcerative colitis developed during pregnancy. In seven, this occurred during the first pregnancy and in one during the second. One of these patients subsequently had two pregnancies. In the remaining 26 patients, the chronic ulcerative colitis antedated the onset of pregnancy for varying periods, viz., 3 to 8 months, 5 cases; 1 to 2 years, 6 cases; 2 to 3 years, 4 cases; 4 years, 2 cases; 5 years, 4 cases; 6 to 7 years, 2 cases. In three instances, the disease started during the puerperium, possibly as intramural hospital acute Shigella infections, and all had subsequent pregnancies (one, one, and three).

The disease was regarded as mild in eleven cases, moderate in twelve, and severe in eleven, depending upon the severity of the symptoms and the degree of bowel pathology as visualized at sigmoidoscopy. In general, the basis of classification was as shown in Table I.

TABLE I. SYMPTOMS AND SIGNS IN 34 PREGNANT WOMEN WITH CHRONIC ULCERATIVE COLITIS

SYMPTOM OR SIGN	MILD	MODERATE	SEVERE
1. Cramps	Occasional	Intermittent	Constant
2. Bowel movements			
(a) Frequency (daily)	3-5	5-10	More than 10
(b) Watery	Usual	Usual	Constant
(c) Bloody	Occasional	Frequent	Constant
(d) Mucopurulent	Occasional	Frequent	Constant
3. Fever	Occasional	Frequent	Frequent
4. At sigmoidoscopy			
(a) Granular, bleeding mucosa	Present	Present	Present
(b) Lymphoid hyperplasia	Present	Present	Obscured by edema
(c) Superficial erosions	Usual	Present	Present
(d) Linear and geographic ulceration	Absent	Occasional	Present
(e) Pseudopolyposis	Absent	Occasional	Present
(f) Mural fibrosis with luminal stenosis	Minimal	Moderate	Advanced
(g) Purulent exudate	Present	Present	Present
5. Number of patients	11	12	11

Most of the patients in this series had corroborative roentgenographic findings. In this connection, it may be stated that roentgenographic study should not supplant sigmoidoscopy. The latter frequently reveals intestinal lesions when the former fails to do so. This is due to the inherent limitations of a diagnostic procedure which photographs a column of barium in an intestine which is distended by the liquid suspension. Superficial defects in mucosal pattern due to ulceration, seen early in the disease, are rarely demonstrable either by a barium enema or postevacuation air insufflation film. This point is stressed because the average physician is hesitant to subject a pregnant patient to sigmoidoscopy. It has been our practice to carry out this examination on pregnant women with the patient in the left Sims' position, using a one-half or three-fourths inch sigmoidoscope. Gentle manipulation of the instrument along the rectosigmoidal curves can usually be carried out until about the fifth or sixth month of gestation. After that, it is unwise to insert the instrument beyond the rectosigmoidal junction since the enlarged uterus impinges upon the pelvic colon and rectum. Proctoscopy can be instituted at any time during pregnancy. It is a valuable procedure in experienced hands, since, in the vast majority of cases, the pathological changes in the intestinal wall involve the rectum as well as the rest of the large intestine. No deleterious effects are produced, particularly if, as we constantly instruct our residents, the instrument is held lightly, like the pen or brush of an artist, and no force is used during insertion or manipulation. By introducing the lubricated index finger into the anus and holding it there for a minute or two before instrumentation, spasm is relieved and the procedure rendered relatively comfortable for the patient. Roentgenographic study is essential for the demonstration of the rare segmental proximal colonic lesions, the extent of colonic involvement, luminal stenosis, or concomitant ileitis.

Effect of Chronic Ulcerative Colitis on Pregnancy

Although a detailed obstetric history in every case was lacking, enough data were available to warrant the conclusion that the presence of ulcerative colitis resulted in no ill effects during either pregnancy or labor. The 43 full-term deliveries resulted in live births in every instance. There were no toxemias of pregnancy or fetal abnormalities except in one case. The mother was seen following her first pregnancy, prior to, and during which, she had a severe chronic ulcerative colitis. We succeeded in recovering *B. dysenteriae* Newcastle (Boyd 88) by mucosal crypt aspiration culture of the mother's bowel. The newborn infant developed diarrhea and we isolated the same organism as that found in the mother. Infection probably occurred during passage of the head over the perineum or from the soiled glove of the obstetrician. The baby made an uneventful recovery. This report is of considerable practical interest, since it has been demonstrated that there is no appreciable transplacental passage of antibodies to *B. dysenteriae* from mother to baby.[4] Newborn infants are quite susceptible to the disease and, if exposed, readily contract it.

Two of the three miscarriages occurred in one patient. There appeared to be no causal relationship between the miscarriages and colitis in either patient. Two therapeutic abortions were performed on one patient before she came under our observations. She had been suffering from severe ulcerative colitis for which an appendicostomy was done. A rectovaginal fistula was also present. Induction of labor was carried out during the sixth month in the case of one patient seriously ill with chronic ulcerative colitis. She subsequently had two pregnancies without untoward results. It is of interest to note that seven of

our patients went through two pregnancies and two through three pregnancies while still in the active phase of the intestinal infection.

Effect of Pregnancy on Chronic Ulcerative Colitis

The status of the patient's colitis was recorded as unchanged, temporarily aggravated, or better. The criteria were the same as those used in Table I. In seven pregnancies (12 per cent) no change was noted; in thirteen pregnancies (30 per cent) the intestinal disease was temporarily aggravated; in twenty-three pregnancies (58 per cent) the intestinal condition was definitely improved, usually to the extent of having few or no intestinal manifestations. These observations apply to both the period of gestation and puerperium. They do not apply, however, to the subsequent course of the disease. In general, it may be said that, compared with nonpregnant controls of approximately the same age, degree of illness, and type of therapy, the subsequent course was almost identical in both groups. There have been no fatalities among the 34 pregnant women. There have been some fatalities among the 387 nonpregnant women (2.8 per cent), but this may be incident to the larger number in the control group. Two pregnant patients deserve special consideration. Both had a severe type of chronic ulcerative colitis but underwent three successful pregnancies following the onset of the colitis. One patient has been completely free of her disease for a period of four years following the birth of her third baby. None of the 34 pregnant women suffered any lasting ill effects from the 43 pregnancies and there was no indication in any case for interruption of gestation, so far as the colitis was concerned. Where there was a temporary aggravation of the intestinal disease (13 pregnancies, 30 per cent), it usually occurred during the first or third trimester and consisted chiefly of an increased number of stools and more profuse intestinal bleeding. It yielded readily to rest and supportive therapy.

Comment

In evaluating the effects of chronic ulcerative colitis on the pregnancy, it appears quite evident that no major obstetric difficulty was encountered in any of the 43 pregnancies occurring in 34 women. In estimating the influence of pregnancy on the ulcerative colitis, it is difficult to escape the conclusion that the colitis was definitely ameliorated in 58 per cent of the pregnancies and unchanged in 12 per cent. If our figures permit broad generalizations, one may assume that in 70 per cent of pregnant women, the presence of chronic ulcerative colitis is certainly no indication for the interruption of pregnancy. In the other 30 per cent, the colitis is only temporarily aggravated and therefore does not militate against the patient going to term. The most striking feature presented by our cases is perhaps not that the patients delivered normally but that almost two-thirds of the pregnancies were associated with improvement of the colitis. The explanation is not obvious. Was the improvement incident to rest, better care, or elimination of disturbing psychological factors? None of these constitutes a valid explanation, or sole explanation, in our cases since the vast majority of our patients in the comparable nonpregnant group appeared to receive the same rest and protective care. Conversely, a number of the pregnant women were definitely annoyed at the additional responsibility involved in having a baby and most of the mothers did not seriously restrict their physical activity until the third trimester. A more valid explanation possibly lies in

enhancement of protective antibodies during pregnancy, particularly against *B. coli,* which, with the enterococcus, constitute the chief secondary intramural invaders responsible for the colitis. While conclusive evidence is lacking, it appears that the characteristic remissions and exacerbations in chronic ulcerative colitis parallel relatively high and low degrees of immunity, as reflected in serologic studies on agglutinins and bacteriostatic activity against *B. coli* and enterococcus.[5] Clinically, exacerbations are often precipitated by upper respiratory infections or similar conditions generally assumed to be associated with lowering of the body resistance. The work of Jeanneney, Castanet and Cator[6] and Frigyesi[7] tends to support the concept of a rising immunity during pregnancy.

The treatment of chronic ulcerative colitis follows the same general principles in pregnant as in nonpregnant[5] women except that active immunization against *B. coli* and enterococcus is not instituted after the fifth month. Supportive therapy consists essentially in the parenteral use of 5 per cent dextrose in normal saline or other suitable electrolytes, amino acids (Parenamine), blood transfusions and lyophile plasma, supplemented by a liberal high protein, high vitamin diet without milk.

A discussion of the pathogenesis of chronic ulcerative colitis is not properly within the scope of this presentation except in so far as it concerns the preventive aspects of the disease. It is our belief, predicated upon data presented elsewhere,[5, 8] that chronic ulcerative colitis and ileitis represent the chronic, nonspecific phase of bacillary dysentery. If this premise is acceptable, the implications are clear. Bacillary dysentery is theoretically a completely preventible disease. Intramural outbreaks and contact infections in hospitals are relatively frequent. Pregnant women should receive the proper sanitary and hygienic safeguards. Rectal tubes should be sterilized after use. Persistent diarrhea in a pregnant women should be promptly investigated by sigmoidoscopy, mucosal crypt aspiration culture and wet smear for cytologic character of the exudate and *E. histolytica.* A purulent cytology generally signifies the presence of bacillary dysentery which also presents a rather distinctive sigmoidoscopic picture. The latter consists of a three-stage progression of pathology, punctate follicular hyperplasia, punctate follicular necrosis, discrete and confluent ulceration on the first, second, and third days, respectively. When positive cultures for the Shigella organisms are obtained, proper therapy should be instituted to eliminate them from the mother. A combination of Sulfasuxidine and sulfadiazine or sulfathiazole should be used, each in dosages of 0.25 Gm. per kg. of body weight. If the mother is a persistent carrier, her baby, as well as others in the nursery, should be protected against contact infections. Failure to observe early isolation precautions in diarrheas complicating pregnancy may prove disastrous. This was exemplified in our hospital where mild diarrhea occurred in a mother a few hours after admission but was not noted until one or two days after delivery. *Salmonella panama* was isolated from the feces but the infant had already been infected, and died within a few days. At necropsy, the same organism was isolated from the blood and intestinal contents of the baby.

Summary

1. An analysis has been presented of 34 patients with chronic ulcerative colitis during 50 pregnancies.

2. Seven pregnancies in five patients did not proceed to term, three of these being operative interferences. All occurred before coming under our observation.

3. Pregnancy was not adversely affected in any of the remaining 43 instances. They resulted in full-term, live births.

4. During 58 per cent of the pregnancies, the ulcerative colitis was definitely improved.

5. From the data presented, it appears that termination of pregnancy is not indicated in the presence of chronic ulcerative colitis.

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CONTINUOUS CAUDAL ANALGESIA

A Report of 1,500 Consecutive Cases

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SINCE the introduction of caudal analgesia by Hingson, Edwards, and Southworth[1, 2] (1942) there have been many individual attempts to evaluate the method. There are, however, no reports of attempts to appraise the value of the method when carried out by resident physicians. With this in mind, the resident house staff has been giving caudal analgesia to suitable patients since July, 1945. The results obtained have been sufficiently gratifying to warrant a comparison with the published reports of more experienced persons.

This report concerns itself with the results obtained in the first 1,500 patients whose labors were conducted under continuous caudal analgesia administered exclusively by the resident house staff. The senior men on the resident staff soon acquired considerable experience in the method so that even though the majority of the caudals were soon being administered by interns, the advice and help of more experienced supervisors were always immediately available.

The over-all success of the method was determined as objectively as possible in each case. An attempt was made to give each caudal a grade. The grades ranged from 100 per cent, when pain was completely relieved between the time when an adequate level of analgesia was reached and the time when the delivery and repair of episiotomy or lacerations were completed, to a zero, when no relief of pain was obtained or when the caudal had to be discontinued prior to completion of the delivery for any reason whatsoever. Cases graded 90 per cent or better were considered as successful, those graded between 50 per cent and 80 per cent as partially successful, and those receiving grades of less than 50 per cent as failures. Segregation of the data in this manner shows that 83.5 per cent of all cases were successful, 3.8 per cent were partially successful and 12.7 per cent were failures. Charting of the results as they were obtained in groups of 100 cases shows that the percentage of successful cases varied from 77 to 93 and the percentage of failures varied from 5 to 21. This demonstrates at a glance what can be expected from caudal when administered by a particular, but changing, house staff. (Fig. 1.)

There were 191 failures in the group. In 98 of these (51.3 per cent) the needle could not be correctly inserted. This figure may seem high, but is only 6.5 per cent of the total number of attempts. In 17 cases, either the needle slipped out of the sacral hiatus, or the tubing became disconnected

without the knowledge the person managing the caudal soon enough to re-establish the level of analgesia prior to delivery. There were ten failures due to faulty anesthetic agent and another ten failures in which the caudal appeared to be satisfactory, but the patient seemed to be emotionally too unstable to permit continuation of the analgesia. The remaining 56 cases include those in which either an adequate level of analgesia could not be maintained or in which an adequate level was never obtained.

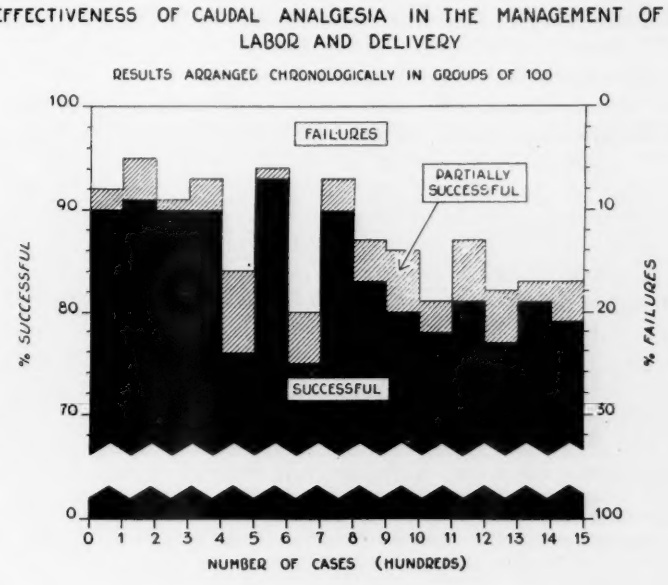

Fig. 1.

In this group of 1,500 deliveries, the effect of continuous caudal on the child was also observed. (Table 1.) One of the reputed advantages of caudal is the promptness of spontaneous cry and respiration of the newborn infant. The results of this study are in complete agreement with that claim. Only 2.5 per cent of the mature children required any resuscitative measures. This figure is quite low, especially when any measure beyond cleaning the nasopharynx with a rubber bulb syringe was considered a resuscitation. Even in the premature group, resuscitation was required in only 6.0 per cent of the group. The figures approximate the figure of 1.9 per cent given by Irving, Berman and Nelson[3] for resuscitation in normal deliveries without anesthesia of any sort. The total number of stillborn infants is somewhat below the expected, but this may be due to the fact that caudal was deliberately not used in many cases in which the baby was known to be dead prior to labor.

The good results in the premature baby are striking. There was a total mortality of only 3.96 per cent in the group weighing 1,001 to 2,500 Gm.

TABLE I. BABIES BORN OF 1,500 MOTHERS IN THE CAUDAL SERIES

SIZE	TOTAL NO.	LIVING	RESUSCITATIONS	STILLBORN	NEONATAL DEATHS
Full term	1,410	1,382	35 (2.5%)	28 (1.9%)	9 (0.63%)
1,001-2,500 Gm.	104	101	6 (6.0%)	3 (2.9%)	4 (3.9%)
500-1,000 Gm.	8	8	0	0	6 (0.75%)
Total	1,522	1,491	41 (2.7%)	31 (2.03%)	19 (1.24%)

Note: This table includes twenty-two sets of twins born during this series of 1,500 deliveries.

This mortality is so low that a comparison between this group and a comparable group delivered without caudal analgesia seemed necessary. Consequently, the record of all of the labors resulting in the birth of premature infants and conducted without caudal analgesia during the same period of time as our caudal group were analyzed. These results are given in Table II.

TABLE II. PREMATURE INFANTS: CAUDAL ANALGESIA VERSUS ALL OTHER METHODS USED DURING THE SAME PERIOD OF TIME

WT. (GM.)	NO.	PER CENT[2]	I.P.[1]	P.P.[1]	PER CENT	N.N.[1]	PER CENT	TOTAL INFANT MORTALITY PER CENT[3]
Caudal Group—1,500 cases. (Total incidence of prematurity, 7.47 per cent)[4]								
2,001-2,500	69	63.30	0	0	0	1	1.44	1.44
1,001-2,000	32	29.36	0	0	0	3	9.37	9.37
Subtotal	101	92.66	0	0	0	4	3.96	3.96
500-1,000	8	7.34	0	0	0	6	75.00	75.00
Total	109	100.				10	9.17	9.17
Noncaudal Group—4,123 cases. (Total incidence of prematurity 6.48 per cent)[5]								
2,001-2,500	152	63.07	4	2	3.95	6	3.95	7.90
1,001-2,000	73	30.29	6	1	9.59	14	19.18	28.77
Subtotal	225	93.36	10	3	5.77	20	8.88	14.66
500-1,000	16	6.64	8	6	75.00	2	25.00	100.00
Total	241	100.00	18	9		22	9.96	20.36

[1]I.P. Death during labor.
P.P. Born living, but not surviving long enough to reach nursery.
N.N. Surviving long enough to reach nursery, but dying before discharge from hospital.
[2]This column gives the per cent distribution of the infants by weight in the caudal and noncaudal group.
[3]This column gives the per cent mortality within the group.
[4]Incidence includes three infants dead at onset of labor.
[5]Incidence includes 26 infants dead at onset of labor.

In any consideration of differences between two groups, it is, of course, essential that the two groups under comparison be as nearly identical as possible. The total infant mortality in babies living at the onset of labor, in the 101 babies weighing between 1,001 and 2,500 Gm., born of mothers receiving caudal analgesia, was 3.96 per cent, whereas the mortality in the 225 babies in the similar group born of mothers not receiving caudal was 14.66 per cent. This difference is considerable, but it is significant only if no selection of cases, either unintentional or otherwise, was practiced which would favor good results in the caudal group and poor results in the noncaudal group.

In order to establish the essential uniformity of the two groups, the frequency with which prematurity occurred in the two groups and the frequency with which premature babies of a given size appeared in the two groups of prematures was obtained. The incidence of prematures was 7.47 per cent among the 1,500 mothers delivered using caudal analgesia and 6.48 per cent among the 4,123 mothers not receiving caudal. These figures are essentially the same as those reported from other institutions.[4] There is possibly a significant increase in the number in the caudal group because, as experience accumulated, there was an increased tendency to use caudal when the baby was known to be premature. The number of babies dead prior to onset of labor is relatively greater in the noncaudal group (26 in 4,123 cases, or .63 per cent) than in the caudal group (3 in 1,500 cases, or .2 per cent)

because mothers whose babies were known to be dead at the onset of labor were usually not given caudal. These two minor degrees of selection should have no effect on the results obtained. The more important question is one relating to the size of the babies. Were there more premature babies of greater weight in the caudal group than in the noncaudal group? This seems not to have been so. The frequency with which babies of the given weight fell into the three groups was consistent. Babies weighing 2,001 to 2,500 Gm. made up 63.30 per cent of the group whose mothers received caudal and 63.07 per cent of the group whose mothers did not receive caudal. Similarly, in the groups weighing 1,000 to 2,000 Gm. the figures were 29.36 per cent and 30.29 per cent, and in the very small, previable group with weights between 500 and 1,000 Gm. the figures were 7.34 per cent and 6.64 per cent, respectively. This analysis of the two groups serves to establish the essential uniformity of the two groups in so far as weight is concerned.

The results obtained indicate that in premature infants of all sizes, living at the onset of labor, the use of continuous caudal analgesia increases the probability of living throughout the labor and of reaching the nursery alive. All babies in the caudal group lived long enough to reach the nursery. Whereas in the noncaudal group, 5.7 per cent of them either died during labor or lived only a few minutes after birth and, consequently, did not reach the nursery. Secondly, not only are babies more likely to live long enough to reach the nursery, but also their chances of ultimate survival are considerably greater. In the caudal group, only 3.96 per cent died neonatally, whereas 8.88 per cent of the noncaudal group died (1,001 to 2,500 Gm. group). The total infant mortality in infants weighing between 1,001 and 2,500 Gm. at birth was reduced in the caudal group to 3.96 per cent, in contrast to a total mortality of 14.66 per cent in the noncaudal group.

The question, of course, arises concerning the significance of the result. The study has been as objective as possible. All premature infants were cared for in the same nursery without the personnel's being aware of which babies were delivered from mothers receiving caudal analgesia and which were from the noncaudal group. The babies in the two groups were also born during the same period of time. The question regarding significance of the difference between the two groups is, therefore, dependent upon the size of the groups. Are the groups large enough to warrant any conclusions? To get some indication regarding this, the groups were divided into equal parts. There were 323 living premature infants admitted to the nursery during the period of study (not including 27 intrapartum and immediate postpartum deaths, all of which occurred in the noncaudal group). When these are divided chronologically into halves, the caudal group was found to contain 46 prematures with two deaths in the first part and 55 prematures with two deaths in the second group (excluding those infants in the previable group). The noncaudal group contained 111 with 11 deaths in the first part and 101 with nine deaths in the second part. The groups can, therefore, be divided in two approximately equal parts with virtually the same results obtained in each. This, of course, suggests rather strongly that the number of cases is adequate to give results which may be expected to recur regularly and which are presumably significant.

Another question, and certainly a most important one, is whether or not continuous caudal analgesia is a worthy substitute for other methods of analgesia and anesthesia, or, if not a substitute, a worth-while adjunct to them. The answer to this is, of course, dependent almost entirely upon the safety of the method as employed, regardless of the degree of technical competence of the persons giving the caudal.

The experience gained in this study has been sufficient to bring to light the majority of complications which may arise. The needle has broken in three cases, in each of which it was necessary to make a short skin incision over the sacrum before the needle could be successfully removed. In two cases, an occult subarachnoid tap occurred so that unintentional spinal anesthesia was obtained. In one of these it was necessary to withdraw spinal fluid through a lumbar tap because 375 mg. of Metycaine had been given. Infection occurred at the site of puncture in five cases and in two of these incision and drainage were necessary. There were seventeen patients in whom the blood pressure was so labile that, despite the use of vasopressor drugs and change in posture, it was deemed wise to discontinue the caudal. Finally, and of not too much importance as judged by the result, a very significant increase in the frequency of delivery by forceps was noted.

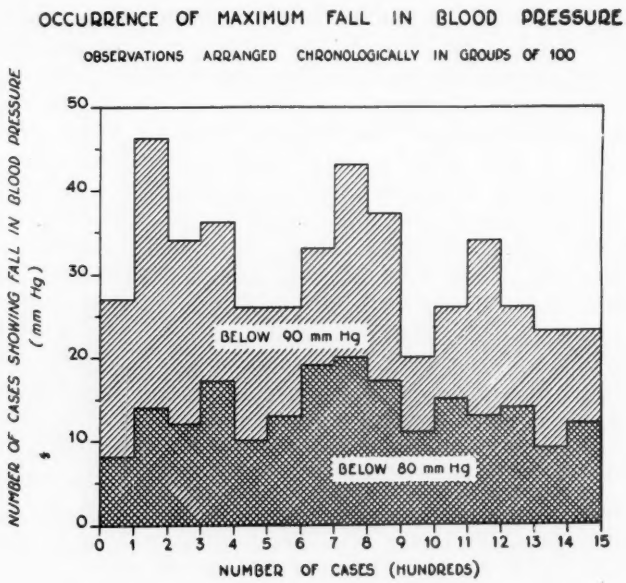
OCCURRENCE OF MAXIMUM FALL IN BLOOD PRESSURE
OBSERVATIONS ARRANGED CHRONOLOGICALLY IN GROUPS OF 100
NUMBER OF CASES SHOWING FALL IN BLOOD PRESSURE (mm Hg)
50
40
30
20
10
0
BELOW 90 mm Hg
BELOW 80 mm Hg
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
NUMBER OF CASES (HUNDREDS)

Fig. 2.

One of the most undesirable features of caudal is the fall in blood pressure. A fall in systolic blood pressure to 90 mm. Hg or below was observed in 30 per cent of the cases, and a fall to 80 mm. or lower was observed in 13.6 per cent of the 1,500 cases. This may at first sight seem too high. The results graphed chronologically in groups of 100 (Fig. 2), however, seem to indicate that this is to a considerable extent an inherent and predictable accompaniment of continuous caudal analgesia using this particular analgesic agent (1.5 per cent Metycaine). In the great majority of these cases in which falls in blood pressure did occur, the pressure soon returned to normal levels with no treatment other than change in posture. Usually, when the patient was placed on her side for a few minutes the blood pressure increased rapidly. That this maneuver was highly satisfactory is well shown by the fact that in the last 1,000 cases only 28 patients received vasopressor drugs, whereas in the first 500 cases 57 patients were given vasopressor drugs. The marked decrease in the need for vasopressor agents was probably due to the fact that it soon became apparent that there were fewer cases showing severe depression of the blood pressure when the

initial induction was carried out with the patient on her back rather than on the side. By this method, a patient whose pressure fell could be treated very promptly and usually effectively by placing her on her side.

The maternal mortality in this group of cases was quite low. There were two maternal deaths, neither in any way due to the type of analgesia used. One patient with eclampsia died of the disease 48 hours after delivery, and a second patient, who had virtually reduced herself to skin and bones by starvation (anorexia nervosa), died three weeks post partum of acute yellow atrophy of the liver. This gives a maternal mortality rate of 1.33 per 1,000 deliveries, a surprisingly low figure when it is recalled that the group of 1,500 included several difficult problems. There were eight patients with severe pre-eclampsia (systolic blood pressures 200 mm. Hg or more) and five patients with actual eclampsia. From this group there were delivered thirteen living (one set of twins) and one macerated infant, all of those born living, surviving. There were also three patients with active tuberculosis, two with severe asthma, and seven with acute respiratory disease ranging from severe bronchitis to bronchopneumonia. Finally, virtually all of the patient encountered with heart disease during the period were given continuous caudal. There was one case of coarctation of the aorta and three with advanced rheumatic heart disease. Two of these were fibrillating and one was in early heart failure. Each of these patients with heart disease and/or pulmonary disease was delivered without incident and without the development of any postpartum complication.

The risk to the mother seems to be no greater than the risk of other forms of analgesia. The risk to the baby is certainly no greater, and in premature infants seems to be materially less. Consequently, there appeared to be no reason for not continuing the study and thereby gaining added experience with this new method of controlling the pain of childbirth and decreasing, if possible, the dangers connected therewith.

Summary

A detailed study has been made of the results obtained in 1,500 consecutive cases receiving continuous caudal analgesia for the management of labor and delivery. In 80 per cent of the cases in which caudal was attempted, the results were entirely satisfactory. Caudal was used successfully in several cases complicated by cardiac and respiratory disease, and in several cases of pre-eclampsia and eclampsia. The most gratifying results were obtained in premature labors. The mortality in premature infants born of mothers receiving continuous caudal analgesia was only one-third as great as in premature infants born of mothers receiving other types of analgesia and anesthesia.

No serious complications have been encountered in this group of cases. The needle was broken in three cases. Occult subarachnoid tap occurred in two cases. Localized infection occurred at the site of puncture in five cases. The systolic blood pressure fell to 80 mm. or below in 13.6 per cent of the cases, but this was usually promptly restored to normal by change in position or vasopressor drugs.

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SPINAL ANESTHESIA FOR CESAREAN SECTION

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(From the Middlesex Hospital)

WE ARE opposed to the use of spinal anesthesia in major obstetric operations as a single injection procedure but as we have employed fractional spinal anesthesia for cesarean operations at Middlesex Hospital since 1941, without a fatality or serious complication attributable to the anesthesia, it seems worth while to report our experience. We have reviewed the cesarean operations done at Middlesex during the past five years; there are 328 consecutive cases. The operations were performed by five general surgeons and the two obstetricians writing this report. Anesthesia was administered by four physician-anesthetists, all of whom have had wide experience with spinal anesthesia, since most of the abdominal operations at our hospital are performed with the aid of "continuous spinal."

The advantages to the surgeon of operating with the aid of spinal anesthesia are too well known to require elaboration. The excellent relaxation of abdominal musculature, lack of bowel distention, absence of straining on the part of the patient are real contributions to the ease of performing unhurriedly an operation in the lower abdomen. Those of us who were trained to do abdominal surgery under inhalation or local infiltration anesthesia do not need to have those advantages emphasized. In the case of a parturient patient, spinal anesthesia offers the important advantage of obtaining maternal anesthesia with no anesthetic effect upon the baby. This is a vital consideration when the operation is to be performed because of premature separation of the placenta or any other condition in which the baby's oxygen supply is dangerously diminished before operation is begun. The chief disadvantage of spinal anesthesia for cesarean operations is that many pregnant women, for some as yet unexplained reason, are unusually sensitive to anesthetic agents placed in the subarachnoid space and a certain number of such patients will develop severe vasomotor collapse if a single dose of 150 mg. of novocain, or similar drug, is so administered. Fractional or continuous spinal anesthesia eliminates this hazard.

Procedure

The patient receives 1½ grains of Nembutal an hour or two before operation and 1/150 grain of atropine when called to the operating room. When the spinal procedure is about to begin, the blood pressure is determined, after which 50 mg. of ephedrine are administered. With the patient lying on her right side upon a Lemmon's mattress, a spinal puncture is made at the third lumbar interspace, using a special malleable needle which is left in place throughout the operation. 10 c.c. of spinal fluid are withdrawn and mixed with novocain crystals to make a 3 per cent solution. A fine-bore rubber tube is connected with the spinal needle and with the syringe containing the novocain solution. Fifty to 90 mg. of novocain dissolved in spinal fluid are then injected into the subarachnoid space. The patient is placed on her back and her blood pressure determined. If the systolic pressure falls below 100, 2 to 3 c.c. of spinal fluid are

withdrawn. The pressure almost invariably rises within a few minutes to the normal level and rarely drops again with the subsequent injections of the anesthetic agent which are given in 20 to 40 mg. doses as required during the operation.

Often an infusion of saline with 5 per cent glucose is started about the time the operation begins, since many patients wish to "be asleep" during the procedure and it is a simple matter to administer a small dose of Pentothal through the infusion tube as soon as the baby is delivered. Also, blood or plasma can be started quickly if the surgeon encounters unusual hemorrhage during the operation. One-fourth grain morphine or one-third grain Pantopon and 1 c.c. Pitocin are given to the mother as soon as the child is delivered.

In our series of 328, there were only three cases in which the operation was not completed under spinal anesthesia. In one instance, the spinal needle was dislodged while turning the patient from her side to her back, and there were two cases in which the blood pressure, after an initial drop, did not return promptly to normal levels. In all three "failures," the operation proceeded under cyclopropane anesthesia without incident.

In the series, 59 cases (18 per cent) showed a systolic drop in blood pressure below 100 after the initial dose of novocain had been administered but, with the two exceptions noted above, the pressure promptly returned to normal and subsequently, with two exceptions, no further drop in blood pressure was noted with repeated doses of the novocain solution.

Dosage

There is a wide variation among gravid patients in the total amount of novocain required for satisfactory anesthesia. The average total dose (given fractionally) in our series was 130 mg. with a range in total dosage from 50 mg. to 440 mg. Seventeen cases required 75 mg. or less. This marked difference among pregnant patients in the effectiveness of novocain as a spinal anesthetic points up the reason why the drug should not be used during cesarean operations in the "one shot" (150 mg.) manner. In many of our patients, 150 mg. of novocain would not have been sufficient for adequate anesthesia. In the majority of our patients, 150 mg. would have been more than necessary and, in several cases, such a dose might well have precipitated serious vasomotor collapse.

Babies

All the babies in our series were in good condition on delivery with the exception of eleven. Of these eleven, four were hydrocephalic, three were dead because of extensive premature separation of the placenta, two were dead several days before operation, one was a monster and one had multiple congenital defects. In other words, all babies who were normal at the beginning of cesarean section were in good condition upon delivery.

Complications

There were no serious or permanent maternal postoperative complications which could be ascribed to the effects of spinal anesthesia. As in any series of lower abdominal operations, a few patients required catheterization for 24 hours postoperatively and a very occasional patient required catheterization for a longer time. Postoperative distention was not a serious problem except in one patient who had had an extensive premature separation of placenta and postoperatively developed intestinal obstruction which, however, was relieved by the passage of a Miller-Abbott tube. A few patients were distressed with "spinal" headaches but these were generally only moderately severe and vanished after a few hours. Very occasionally, a spinal headache persisted for a few days.

Complications having no relation to the spinal anesthesia are listed briefly for what interest they may present as postoperative results obtained after cesarean operations in a 175 bed hospital where the operations were performed by seven surgeons, most of whom have had no special obstetrical training.

Mortality

Two deaths (0.6 per cent), both from embolism. (One patient, a severe essential hypertensive, was advised to have her pregnancy terminated in the first trimester but refused.)

Morbidity

Fifty-four cases (16.4 per cent). (Excluding the first twenty-four hours after operation, two or more rises of the rectal temperature to 100.4° F. or above constituted a morbid convalescence.) Two to four such elevations of temperature were termed "mild" febrile convalescences; there were 24 cases (7.3 per cent). Four to seven elevations above 100.4° were classified as "moderate"; 28 cases (8.5 per cent). Elevations of longer duration were called "severe"; 2 cases (0.6 per cent).

Classification of the causes of the febrile convalescences is as follows: 3 pyelitis, 3 thrombophlebitis, 2 mastitis (one with abscess), 1 active tuberculosis, 1 evisceration (an obese patient who recovered after resuture of the abdominal wall). In the remainder of the cases (44), mostly "mild," there were no specific diagnoses.

Conclusion

Continuous or fractional spinal anesthesia, when administered by a capable physician-anesthetist, is a safe and, in our experience, the most satisfactory anesthesia for use during cesarean operations.

We are indebted to Dr. Joseph Magnano, chief anesthetist, Middlesex Hospital, for critical evaluation of this report.

THE PREMATURE INFANT

A Study of One Hundred Seventy-Three Liveborn Premature Infants

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THIS paper is based on a study of 7,332 deliveries occurring between the years 1939-1944. During that period, there were 173 living premature infants born, an incidence of 2.35 per cent. The highest incidence of premature delivery occurred in 1944 when 3.22 per cent of 1,487 deliveries were premature (Table I).

The records were reviewed with regard to both the maternal factors involved, and the condition of the infant at birth and at discharge from the hospital. Consequently, the paper has been divided into two parts—the first concerned with the maternal factors; the second with the infant.

TABLE I. NUMBER OF PREMATURE INFANTS DELIVERED BY YEARS. NUMBER AND PERCENTAGE OF FETAL MORTALITY BY YEARS

YEAR	TOTAL NUMBER OF DELIVERIES	NUMBER OF PREMATURE INFANTS BORN	PERCENTAGE OF PREMATURE INFANTS	NUMBER OF PREMATURES DYING	PERCENTAGE OF PREMATURES DYING
1939	856	17	1.97	6	35.29
1940	969	21	2.17	6	28.57
1941	1067	20	1.87	5	25.00
1942	1431	37	2.58	4	10.81
1943	1522	30	1.97	9	30.00
1944	1487	48	3.22	9	18.75
Total	7332	173	2.35	39	22.54

The records are taken from both private and clinic cases, and no attempt has been made to segregate the two types of patient.

Maternal Factors

Age.—The average age of the mothers was 29.9 years. The youngest was 17 years; the oldest 45 years.

Gravida.—Of the women studied, 41.02 per cent were primigravidas. It was noticed that, as the parity of the patient increased, the probability of a premature infant decreased (Fig. 1). In the higher multipara, the occurrence of a premature infant was almost negligible. In the primigravid women, 42.18 per cent of the patients were 27 years of age or over; while 25 per cent of them were 30 years of age or over. It would appear that the older primiparas show a larger proportion of premature deliveries than do the younger primiparas.

Past History.—Of the cases studied, 15.38 per cent gave a history of previous miscarriage or premature delivery.

Prenatal History.—The records were reviewed with particular regard to the prenatal history (Fig. 2). In 39.87 per cent of the cases, no abnormalities of any kind were recorded. Urinalysis and blood pressure were within normal limits; weight gain was not excessive, and the patients did not complain of edema, urinary difficulties, headaches, dizziness or epigastric distress.

Toxemia was recorded in 22.69 per cent of the cases. These cases ranged from the mild toxemias to the fulminating, convulsive type. The fetal mortality in these cases was 16.21 per cent. None of the mothers died.

Staining was observed in 14.10 per cent of the cases. Such staining occurred both in the first and second trimesters of the pregnancy. Hormones were administered in one case with cessation of staining. The remaining cases were treated expectantly with bed rest and sedation.

Spontaneous rupture of the membranes occurred in 6.74 per cent of the cases. A history of injury followed by rupture of the membranes was obtained in only two of the cases. In the remaining nine cases there was no history of injury or strain.

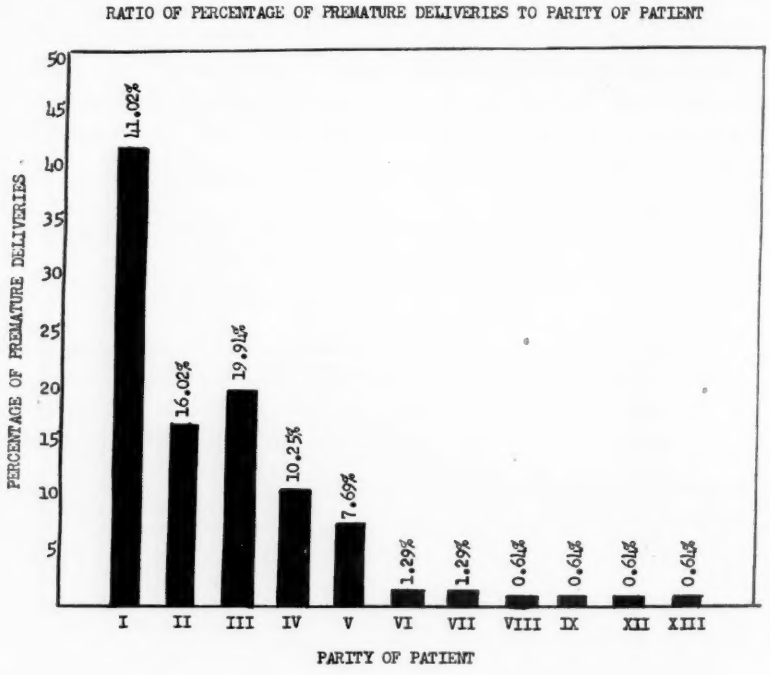

Fig. 1.

Premature separation of the placenta was noted in 4.90 per cent of the cases. Placenta previa occurred in one case.

A variety of other diseases occurred, among which was one case each of pyelitis, renal calculus, bilateral hydronephrosis and hydroureter, congenital heart disease (patent ductus arteriosus), rheumatic heart disease, grippe, bronchitis, Reynaud's disease and scleroderma, scarlet fever (one month prior to delivery) and endometriosis. Appendectomy was performed eight days prior to delivery in one case. There were two recorded instances of fibroid uteri (Fig. 2).

Days Prior to Expected Date of Confinement.—Of these patients, 25.67 per cent were at term; 48.64 per cent were about 60 days from term; 8.10 per cent were about 90 days from term; while 4.05 per cent were about 120 days from term. The expected date of confinement could not be accurately determined in 13.54 per cent of the cases. These patients were unable to state with any degree of accuracy the date of their last menstrual periods.

Multiple Pregnancy.—Multiple pregnancy occurred in 10.98 per cent of the total number of births. All were twin births. Female twins occurred in 78.94

per cent of the cases. Male twins were observed in 10.52 per cent of the cases. Mixed twins (i.e., one male and one female) occurred in 10.52 per cent of the births.

Delivery and Labor.—Delivery from below was accomplished in 84.39 per cent of the cases; cesarean section was performed in 15.61 per cent of the cases (Table II).

TABLE II. FETAL MORTALITY IN VERTEX AND BREECH PRESENTATION AND CESAREAN SECTION

PRESENTATION	NUMBER OF BIRTHS		NUMBER OF DEATHS	FETAL MORTALITY (PER CENT)
	NUMBER	PER CENT		
Vertex	130	75.14	22	21.2
Breech	16	9.24	6	37.5
Cesarean section	27	15.62	11	40.7

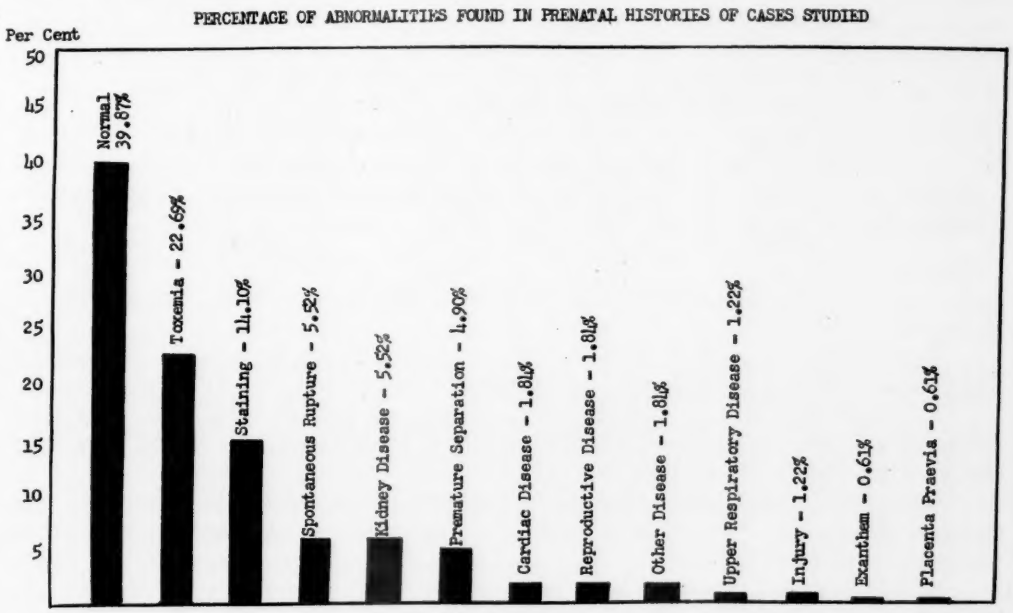

Fig. 2.

Vertex presentation was observed in 75.14 per cent; breech presentation in 9.24 per cent.

A fetal mortality of 21.2 per cent occurred with vertex presentation. Breech presentation was accompanied by a 37.5 per cent fetal mortality. Cesarean section showed the highest fetal mortality, that of 40.7 per cent of the cases.

The average length of labor was 7.98 hours. The longest labor observed was 48 hours.

Month of Delivery.—Premature deliveries showed no particular predilection for certain months of the year. January and February had the smallest number, while October and November had the greatest.

One curious situation was observed, however. The largest number of premature deliveries occurred in 1944, at which time 48 premature infants were born. Of these, 36 occurred after June 6, 1944, the day of the invasion of Europe. Nearly half of these (47.2 per cent) occurred in primiparas, whose husbands were of an age compatible with military service standards. Of these

cases, 89 per cent were listed as having a normal prenatal course. Perhaps some correlation exists between the psychological well-being of the expectant mother and the incidence of premature deliveries.

Fetal Factors

Mortality.—There was an average of 22.54 per cent deaths for premature infants in the cases studied. Births and deaths by weight have been tabulated and are shown in Table III. (The weight of these infants was recorded in pounds, and the author has retained those figures, although also converting the weight to grams.) In the conversion of pounds to grams, 450 Gm. have been used as being equal to one pound. The results obtained in this study are in accord with those published by Breese,[1] namely, that the weight of the child is the most important single factor in prognosis. As the weight of the child increases, the mortality factor decreases. There was a 100 per cent mortality observed in children born weighing 1½ pounds (675 grams) or less, while those weighing between 4½ and 5½ pounds (2,025-2,475 Gm.) showed but a 7.14 per cent mortality.

TABLE III. NUMBER OF BIRTHS AND DEATHS BY WEIGHT

WEIGHT	(675 GM.) 1½ LB. OR UNDER	(675-1225 GM.) 1½-2½ LB.	(1225-1575 GM.) 2½-3½ LB.	(1575-2025 GM.) 3½-4½ LB.	(2025-2475 GM.) 4½-5½ LB.
Births	4 (2.31%)	14 (8.09%)	29 (16.76%)	70 (40.46%)	56 (32.35%)
Deaths	4 (100%)	11 (78.57%)	12 (41.37%)	8 (11.42%)	4 (7.14%)

The largest number of infants (40 to 46 per cent) born weighed between 3½ and 4½ pounds, and the mortality rate in this group was 11.42 per cent.

It would appear that certain of these infants, particularly those weighing between 4½ and 5½ pounds (2,025-2,475 Gm.), could well be called immature rather than premature infants.

Length of Babies.—The average length of the infants was 17.54 inches. The shortest infant was 12 inches long; the longest 20. The largest number (30.95 per cent) measured 18 inches.

Initial Temperatures.—Rectal temperatures were taken on all of the infants, and an average initial temperature of 96.96° F. was obtained. Twelve infants had temperatures of 100° F. or over. The highest recorded temperature was 102° F. The temperature in the majority of cases rose on the second day to 99° F., and maintained it. Infants showing a slow rise in temperature up to 99° F. usually had a more difficult time than those in whom the temperature rose on the second day.

Initial Weight Loss.—The average initial weight loss was 3.38 ounces. Of the infants, 40.4 per cent showed no initial weight loss. The greatest weight loss was 25 ounces. This occurred in an infant weighing 4 pounds 12 ounces at birth. The child survived and was discharged on the fifty-eighth hospital day.

Length of Hospital Stay.—There was an average of 11.9 days spent in the hospital following delivery. The longest period of hospitalization noted was 87 days; the shortest 7 days.

Weight Gain on Discharge.—These infants gained an average of 9.7 ounces during their hospital stay. Once the initial weight loss had been overcome, the weight gain was progressive.

There was one recorded instance of diarrhea in this group; the remainder of the infants averaged two to three stools daily.

The feeding of these infants varied with the individual pediatrician. All infants, however, were given vitamin K intramuscularly following delivery. Vitamin K was not given to the mothers before delivery.

Autopsies were performed on nine of the infants who died. Atelectasis was reported as the cause of death in three cases. Atelectasis plus cerebral hemorrhage were given as the cause of death in two cases. Cerebral hemorrhage plus pneumonia accounted for two deaths; pneumonia alone was responsible for one death; and edema of the pia-arachnoid plus congestion of liver, spleen, kidneys and both adrenal medullas accounted for one death.

Summary

A study of 173 premature infants is presented. Maternal factors and fetal factors are recorded.

Premature delivery occurred most frequently in primigravidas in the older age group.

Over one-third of the cases studied showed no abnormalities during the prenatal period. Toxemia was recorded in approximately one-fifth of the cases. One-sixth of the cases gave a history of staining. Spontaneous rupture of the membranes with and without history of injury and premature separation of the placenta was observed in approximately 10 per cent of the cases.

One-quarter of the patients (25.67 per cent) were at term. Approximately 50 per cent were about 60 days from term.

Multiple pregnancy occurred in 10 per cent of the cases.

Delivery from below was effected in 85 per cent of the cases. Cesarean section was performed in 15 per cent.

Fetal mortality was highest in cesarean section (40.7 per cent); next highest in breech extraction (37.5 per cent). Vertex presentation was accompanied by a fetal mortality of 21.2 per cent. The average length of labor was 7.98 hours.

The highest percentage of premature deliveries occurred in the year 1944, and the majority of these after June 6, 1944. The possibility of psychogenic factors in premature delivery must be considered.

An average fetal mortality of 22.54 per cent was observed. It was noticed that as the weight of a child at birth increased, the probability of death decreased.

Length, weight, and initial temperature of the infants are recorded.

Initial weight loss, length of hospital stay, and weight gain on discharge are recorded.

Autopsy reports on nine cases are summarized.

Reference

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TORSION OF THE HYDATID OF MORGAGNI*

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ONE frequently observes small pedunculated cystic structures in the region of the tubal fimbriae. These appendages, known as the hydatids of Morgagni, usually arouse little more than passing attention. In 1906, Kelly[1] remarked that, although he had seen a variety of interesting affections associated with such structures, he had never observed a condition which could interfere with health. He then described true knots along the pedicle without interference with circulation, strangulation of a portion of the fimbria, hemorrhagic infarction due to twisted pedicle, and adhesions of the hydatid to the sigmoid. In the same year, Boldt[2] reported a large hydatid (3 by 3¾ inches) with torsion of 180 degrees, involving the tube. The only complaint was left lower quadrant pain. In 1910, Grauert[3] operated upon a patient for chronic appendicitis, only to find a plum-sized right hydatid twisted 360 degrees on its pedicle. Subsequently, Andrews[4] in 1912, Waters[5] in 1919, and Abernathy[6] in 1929 reported acute symptoms associated with torsion of the pedicle of the vesicular appendage, each believing his case report to be the first in the literature. To date, a careful review of the world literature reveals twenty-one references to torsion of the hydatid of Morgagni (Table I), although, in four instances, no details are available. (Kelly,[1] Meigs,[7] and Waugh[8]). In spite of these reports, Novak,[9] in 1947, states that the hydatid has no especial clinical significance except in very rare instances of intestinal angulation and obstruction caused by a long pedicle.

Case Reports

To the cases already reported, we are adding five more. These were patients operated upon at Michael Reese Hospital during the past ten years, three in our private practice. By analyzing this total of twenty-two case reports, in which more or less complete information is available, we hope to present a clinical picture by which torsion of the hydatid of Morgagni can be recognized. In no instance to date has the possibility of such pathology been entertained pre-operatively. However, since three such cases were reported as having been operated upon at the Mayo Clinic within a two-year period and four of our five patients within a three-year period, the condition must be more common than the literature indicates.

Typically, the hydatid of Morgagni is a small oval or spherical structure about 8 mm. in diameter. Often there is an area of constriction in the mid-portion that produces a dumbbell or beanlike shape. It is usually single but may be multiple. It may be sessile or have a pedicle up to 12 cm. long, although the average length is about 3 cm., and the average thickness is 2 mm. While the exact origin is still debated, it is usually accepted that these cysts represent the persistent cephalad portion of the Wolffian duct. According to Gardner, Greene and Peckham,[20] these cysts arise from mesonephric tubules

*Read at a meeting of the Chicago Gynecological Society, Nov. 21, 1947.

or ducts or from paramesonephric structures. Since other broad ligament cysts, whether intraligamentous or pedunculated, may have similar origins, they believe it desirable to avoid such terms as hydatid of Morgagni, Kobelt cyst, or parovarian cyst, and to base the terminology solely on microscopic findings. Unfortunately, in the cases herein reported, this is impossible since these structures were all necrosed. Thus, we can only refer to them as cystic appendages, commonly known as hydatids of Morgagni.

When torsion occurred, pain was the most frequent complaint. In at least one instance, however, pain was lacking, although a tiny twisted gangrenous hydatid was found incidentally during unrelated surgery. At the onset the pain was often diffuse, later becoming localized to the right or left lower quadrant. The intensity varied from mild to severe and the duration from a few hours to days. The only characteristic quality of the pain was its colicky or cramplike nature, which was noted by almost all authors. Not infrequently, an antecedent history of previous attacks, over a period of from weeks to years, was elicited. In about 25 per cent of the patients, onset of dysmenorrhea dated from the first attack of pain. Such dysmenorrhea has been observed to disappear following removal of the hydatid. Nausea and vomiting occurred in 50 per cent of all patients.

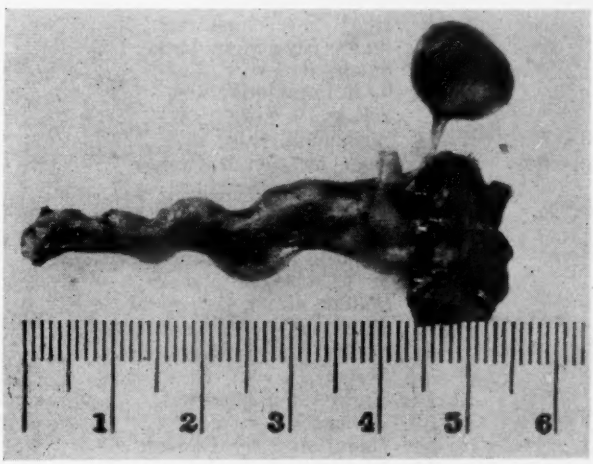

Fig. 1.

Physical examination was not significant. Some patients were acutely ill and evidenced considerable discomfort but no patient appeared seriously ill. The abdomen was occasionally distended, usually tender, and sometimes rigid over the involved area. In only three instances did the temperature exceed 101° F. or the pulse 100. Leucocytosis varied from 9,200 to 21,000, averaging about 15,000. There was no correlation between symptoms, findings, and blood count.

In fourteen of the twenty-two cases, the hydatid was right-sided. This apparent predilection for the right is probably indicative of greater anxiety over right lower quadrant pain because of fear of appendicitis. As a result, exploratory operation is more frequently performed for right-sided complaints and more right-sided twisted hydatids are discovered. Left-sided involvement was variously diagnosed as left-sided appendicitis, twisted left ovarian cyst and ectopic pregnancy.

TABLE

NO.	YEAR	AUTHOR	AGE	SYMPTOMS		
				PAIN	NAUSEA AND VOMITING	MISCELLANEOUS
1	Before 1906	Kelly				
2	1906	Boldt	43	Left lower quadrant, 2 years		Dysmenorrhea
3	1910	Grauert		Right lower quadrant, long time		
4	1912	Andrews	36	Right lower quadrant, 5 days	0	
5	1919	Waters	18	Left abdomen, cramp-like, watched 5 days	+	Dysmenorrhea,
6	1929	Abernathy	33	Right lower quadrant, 3 weeks, colicky		Similar attack 8 years before
7	1930	Okinczyc[10]		Right lower quadrant, 5 hours, severe, sudden, general at first		
8	1931	Heinrich[11]	15	Lower abdomen, cramp-like, tender right side, 1 day	+	Dysmenorrhea,
9	1934	McDermott[12]	16	General abdominal, right lower quadrant 5 hours, rigid right lower quadrant		
10	1936	Mugnai[13]	23	Left lower quadrant, colicky, 1 year		
11	1936	Tailhefer[14] & Adrianopoulo	30	Abdominal pain, 15 days, location left lower quadrant, cramplike		
12	1936	Tractenberg[15]	29	Abdominal pain 2 months, tender left lower quadrant	+	Mass palpable, distention, rebound
13	1937	Gregorová[16]	38	Right lower quadrant pain, 1 yr. repeated attacks	+	Distention 4 months mass palpable
14	1937	Zener[17]	13	Sudden attack abdominal pain, right lower quadrant	+	Tender McBurney's point
15	1937	Zener	34	Severe, left-sided cramp-like		Palpable mass, dysmenorrhea,
16	1938	Bowles[18]	16	Right lower quadrant, 6 months	+	Distention, rigid McBurney's point
17		Meigs		(Mentioned by Bowles)		
18	1939	Waugh	22	Right lower quadrant, 24 hours, persistent	0	McBurney tender and rebound
19	1939	Waugh				
20	1939	Waugh				
21	1943	Howser and River[19]	14	Right lower quadrant, 19 hours, cramplike	+	Tender McBurney's point becoming rigid 8°
22	1947	Reis and DeCosta	35	General abdominal, 12 hours, achy	0	Tender right umbil.
23	1947	Reis and DeCosta	28	Severe left lower quadrant pain, few hours		Cyst left, felt 6 months before
24	1947	Reis and DeCosta	38	0	0	Walked into hospital
25	1947	Reis and DeCosta (d)	23	Right lower quadrant, moderate, 3 months especially 1 week	0	Walked into hospital, not acutely ill
26	1947	Reis and DeCosta (e)	33	Right lower quadrant, intermittent, 15 years, especially 3 months	N	Walked in, not acutely ill.

(d) Courtesy Dr. Irving Stein.
(e) Courtesy Dr. Herman Strauss.

I

PREGNANT	PRE-OPERATIVE DIAG.			TEMP.	WHITE BLOOD COUNT	PULSE	OPERATIVE FINDINGS		
	APPENDICITIS	TWISTED CYST	MISCELLANEOUS				RIGHT	LEFT	FLUID
		x						x	
	x						x		
6 months		x		98.6°F.		80	x		
	x left sided		or hemorrhage into cyst	to 101°F.	16,800	to 130		x	x
2 months			Abortion Oophoritis	99.4°F.		80	x		
	? x		or tubal pregnancy	35.9°C.			x		x
	? x			100.8°F.	9,200	92	x		
	x			99°F.		96	x		x
			Adnexitis, Tbc.					x	
2½ months			No. definite diagnosis	40°C.		100		x	
			Ectopic pregnancy	101.2°F.	13,500	120		x	x
4 months		x					x		
	x				14,600		x		x
		x						x	
	x			99.6°F.	21,000		x		x
	x				12,000		x		
	x			99.8°F.	16,500 18,500	68 74	x		x
7 months	x			99.6°F.	19,400	96	x		
		x		100.2°F.	13,600	116		x	
			Fibroids	100.2°F.	9,300	90	x		
		x		99.8°F.	9,700	92	x		
	x			98°F.	9,750	72		x	

Of twenty patients in whom the age is known, the youngest was thirteen and the oldest forty-three, with eleven patients under thirty. Five patients were pregnant from two to seven months. Still, we do not believe that pregnancy is a predisposing factor. Rather, pregnant women probably are more concerned about themselves and their physicians are more solicitous.

Examination of the removed tissue has yielded little information indicative of etiology since such tissue is generally necrosed and difficult to recognize as any specific structure.

Torsion of a hydatid, even when associated with gangrene, does not lead to serious intra-abdominal disease. Since the tissue involved is small and usually not adherent to the bowel, one can expect aseptic necrosis to occur with slight degrees of peritoneal reaction. No patient has ever been known to die from failure to operate upon a twisted hydatid. It is probable that patients occasionally operated upon with a diagnosis of acute appendicitis actually suffer from a small twisted gangrenous hydatid which is overlooked. The McBurney incision does not lend itself to thorough inspection of the pelvis. The frequently reported presence of serosanguineous fluid in the abdomen should make one very suspicious of pathology other than the appendix. With bloody peritoneal fluid, the adnexae must be inspected, including the fimbriated region.

Clinically, the five patients we report fall into three classes. Two suffered acute pain, without nausea and vomiting, and were operated upon within a few hours. One was diagnosed as acute appendicitis and the other as a twisted left ovarian cyst. Two other patients complained of intermittent right lower quadrant pain over a period of years. These patients were not in acute distress on admission and were studied in the hospital prior to surgery. One was diagnosed, after transabdominal pneumoperitoneal roentgenogram, as a twisted right ovarian cyst. The other was considered to have recurrent appendicitis. This patient had a gangrenous left-sided hydatid although pain was referred solely to the right side. The last patient presents a unique situation. She entered the hospital without abdominal distress, for hysterectomy because of fibroids. The finding of a small, twisted, gangrenous hydatid was incidental. It points out, however, that asymptomatic gangrene can occur.

Bimanual findings were not helpful. In one patient, previously known to have a cystic adnexal mass, the diagnosis was twisted ovarian cyst. The mass proved to be a large hydatid of Morgagni. In the other patients, there was only tenderness. On abdominal palpation, tenderness was noted in either right or left lower quadrant. Rectus muscle rigidity was not observed in this group.

A gangrenous hydatid was removed from each of these patients. The size varied from 5 to 25 mm. and the pedicle from 10 to 25 mm. In no patient did the temperature exceed 100.2° F., and in only one was the pulse over 100. The two patients with acute symptoms had white blood counts of 13,000 to 19,400, while the other three were from 9,300 to 9,750.

Conclusions

1. The symptoms arising from torsion of a hydatid of Morgagni closely resemble those of acute appendicitis, if right-sided. The pain, however, is usually colicky and has been intermittently present over a period of time. The patient is usually not so sick as to seek early medical care. Nausea and vomiting are frequently present. The temperature usually is less than 101° F. and the pulse under 96.

2. The pelvic organs should be examined at every laparotomy. This becomes increasingly important when serosanguineous fluid is encountered. If a McBurney incision has been used, it may require extension to make such examination possible.

3. Pedunculated hydatids of Morgagni encountered during surgical procedures should be removed prophylactically.

4. Torsion and even gangrene can occur with few if any complaints.

5. Although only a total of twenty-six cases of torsion of the hydatid of Morgagni have been reported, the condition probably occurs fairly frequently; at times it may be overlooked, at other times misdiagnosed.

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Discussion

DR. FRED O. PRIEST.—The pedunculated hydatid is relatively common as seen in pelvic surgery. Torsion with acute symptoms might be expected to be relatively common but this is not true. In reviewing the records at the Presbyterian Hospital, I could find only three cases occurring since 1930. In none of them was a correct preoperative diagnosis made, acute appendicitis or twisted ovarian cyst being suspected. The fact that more have been found on the right side is probably due to the fact that "right-sided" abdominal pain is regarded more seriously and surgery is advised, while pain in the left lower quadrant is often treated conservatively.

The presence of straw-colored or blood-tinged fluid was not mentioned in any of the three operative records that I am reporting. The presence of such fluid, varying from a few cubic centimeters up to one ounce or more, was recorded over a period of two years. We found that it bore a definite relationship to the age of recent corpora lutea, whether or not hydatids were present.

The first of our patients: Mrs. E. K., aged 27 years, para 1, gravida 1, had had 4 previous attacks of colicky pain in the right lower quadrant. Nausea and vomiting occurred with the attack. On admission, her temperature was 99.2° F., her white blood cell count 12,000, and there was moderate rigidity in the right lower quadrant. A plum-size gangrenous hydatid and a normal appendix were removed at laparotomy.

The second: Mrs. J. K., Aged 30 years, para 0, Gravida 0, was first studied by the genitourinary service with negative findings. She had knifelike, spasmodic pain in the left lower quadrant. On posterior colpotomy incision, a walnut-size hydatid, twisted on its pedicle from the left tube, was found lying in the cul-de-sac.

The third patient: Mrs. J. A., age 31 years, para i, gravida ii, entered the hospital at the beginning of her ninth month of pregnancy. She complained of nausea, vomiting, and knifelike pain in the right side at the level of the umbilicus. Her temperature was 100.2° F. and her white blood cell count 16,000. Acute appendicitis was diagnosed and she was operated upon through a muscle-splitting incision. The appendix was found normal and was left in; a walnut-sized twisted hydatid was removed from the right tube. She delivered normally, thirty-six hours later, and made an uneventful recovery.

DR. R. R. GREENE.—The term "paramesonephric duct" makes good sense. Gruenwald has very beutifully demonstrated that its advancing tip grows under the basement membrane of the mesonephric duct. He has also shown that its normal development is dependent on the presence of the mesonephric duct.

The development of the oviduct fimbria is a very complex process. Because of this very complexity, aberrant epithelial structures of paramesonephric origin are frequently found in or on the broad ligament. The "hydatid of Morgagni" or better termed "pedunculated paromesonephric cyst" is such a structure. Its mode of origin can easily be demonstrated in the embryo. In properly prepared tissues from the adult, its paramesonephric derivation also can be easily demonstrated. Its epithelium is identical to that of the oviduct and is distinctly different from that of mesonephric tubule or mesonephric duct origin.

The differences between the epithelia of paramesonephric and mesonephric origin have been discussed in some detail in a publication by Drs. Gardner, Greene, and Peckham in a recent issue of this Journal.

DR. REIS (Closing).—The occurrence of these twisted cysts of Morgagni or mesonephric remnants in the course of several years stimulated us to make this report. We hope to find out whether they are as infrequent as the literature leads us to believe. Secondly, we would like to emphasize that, when the patient is operated upon for what seems to be a ruptured appendix or a twisted ovarian cyst and nothing is found, it is much more satisfying to find the cause of the trouble to be a twisted hydatid of Morgagni rather than to close the abdomen without having found any pathology to account for the symptoms for which the laparotomy was performed.

NONOPERATIVE TREATMENT OF URINARY INCONTINENCE IN WOMEN*

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INCONTINENCE may vary from mere dribbling on occasions to complete loss of urinary control at all times. Just as there is a variation in sensitivity to pain, so is there a difference in the reaction of individuals to loss of bladder control. "Stress incontinence"[1, 2] indicates loss of urine under various circumstances related to effort on the part of the patient, such as lifting, coughing, sneezing, etc. It is these cases which are properly subjected to operative treatment; but clinically, true stress incontinence is difficult to differentiate from false incontinence caused by irritative lesions in the bladder or urethra.

One of the commonest causes of urinary complaints in the female, which may be present from early infancy throughout life, is a papillary posterior urethritis due to infection in the glands near the vesical orifice. Folsom[4] believed that this infection may take place during the diaper stage of life. Infections of various types, ascending from the vulva and vagina, may create inflammatory lesions in the urethra and bladder. Among the etiologic agents, the trichomonas, Monilia, and many varieties of bacteria may cause irritative lesions resulting in false incontinence.

No satisfactory test has been devised to determine whether a patient has true or false incontinence. X-ray studies, cystometric readings, endoscopy, and cystoscopy have all proved of little value in differentiating true from false incontinence. A test commonly used to detect incontinence in women is performed by instilling 250 c.c. of saline into the bladder and having the patient cough or strain while in the lithotomy and erect positions. However, during this test the patient may voluntarily close her external sphincters and prevent leakage, while under ordinary conditions when she sneezes, lifts a heavy object or coughs, she is not on her guard to prevent bladder loss.[3] For this reason, this test should not be used as a reliable index to determine incontinence.

At the present time the treatment of urinary incontinence in women is largely surgical, attempting by operative measures to restore damaged structure and function. Occasionally women who have had excellent technical operative repairs for supposed stress incontinence may remain incontinent because their loss of bladder control was never due to true "stress incontinence." Other patients, following operation for cystocele without incontinence, have developed incontinence after well-conceived and well-executed operative measures. The incontinence in many of the latter cases is believed to be due to irritative lesions in the bladder or urethra, or both, created by the operation; and thus should be classified as false incontinence. Sometimes true "stress incontinence" is present together with false incontinence.

*Read before the Section of Obstetrics and Gynecology on Oct. 28, 1947, at the Academy of Medicine.

Although there have been no adequate clinical tests to differentiate false from true incontinence, the following therapeutic method has proved satisfactory. It can be used as an aid in selecting cases of incontinence which require surgery. In many cases the incontinence may be cured by this method alone. Incontinence may return as a result of a recurrence of the original inflammatory lesions.

A course of treatment by dilatation of the urethra with graded Hegar dilators from No. 6 to No. 9 is given once weekly. After the urethra has been dilated for approximately five minutes, the bladder is emptied with a catheter, and 5 per cent silver nitrate on a long applicator is applied topically, with or without an endoscope, to the trigone, bladder neck, and urethra, as described by Oberlander[5] and Kelly and Burnam.[6]

An attempt is made to strengthen the voluntary urinary sphincters by instructing the patient to start and stop the urinary stream several times during micturition. Ephedrine (25 mg.) is prescribed three times a day for its sympatheticomimetic action. This drug contracts the internal sphincter and at the same time is a powerful depressant of vesical function.[7]

The material analyzed consisted of 175 consecutive cases seen at the Beth Israel Hospital Female Urologic Clinic from March, 1941, to March, 1947. The majority of the patients were intradepartmental referrals, presenting urologic symptoms, often after some form of surgery had been performed on the vaginal walls. Many of these patients presented cases of incontinence which had been treated surgically for the cure of this symptom. Some of the others had various types of vaginal surgery. Among these 175 cases, 82 patients presented themselves with the chief symptom of urinary incontinence, with or without other urologic complaints. The high incidence of incontinence in this series may appear unusual when compared to similar studies reported elsewhere. However, it must be kept in mind that this group was a hand-picked series selected for the analysis and treatment of urinary complaints usually in older women, often occurring after operations for cystocele.

Although urinary incontinence in the majority of women is due to injuries incurred during parturition, the symptoms often fail to make their appearance until after the menopause. Seventy-six per cent of the patients in this group fell into either the menopausal or postmenopausal decades. Of the 82 incontinent cases, 70, or 85 per cent, were between 41 and 70 years of age.

Cases were classified as to the degree of incontinence,[8] as shown in Table I.

TABLE I

	NUMBER OF PATIENTS
Mild incontinence occurs paroxysmally on stress following lifting, coughing, or sneezing	50
Moderate grade of incontinence occurs regularly following any form of exertion	27
Marked incontinence occurs on change of position	4
Complete incontinence is inability to retain urine in the bladder regardless of position	1

The cases can be grouped further clinically as follows:

Group I. Cases of incontinence which had had no previous vaginal surgery.

Group II. Patients in whom incontinence first appeared after vaginal surgery.

Group III. Cases following vaginal surgery who although preoperative incontinence had been noted, had had no specific operative procedure for its cure.

Group IV. Cases of incontinence who had had vaginal surgery for the cure of incontinence with failure.

TABLE II. DURATION OF THERAPY

1 month	22 cases
2 to 3 months	21 cases
3 to 6 months	14 cases
6 to 18 months	11 cases
	68 cases
Did not return	14 cases
Total	82 cases

The results of treatment are indicated in Table III.

TABLE III. ANALYSIS OF CASES

	NUMBER OF CASES	ANTERIOR VAGINAL WALL			RESULTS OF THERAPY			
		ADEQUATE	CYSTOCELE	OVERCORRECTED	CURED	IMPROVED	FAILURE	NOT RETURNED
Group I. No surgery	30	11	19	0	9	12	5	4
Group II. Postoperative incontinence No preoperative incontinence	14	8	4	2	3	4	4	3
Group III. Untreated preoperative incontinence	15	10	3	2	7	5	0	3
Group IV. Incontinence not cured by surgery	23	15	2	6	8	7	4	4
Total	82	44	28	10	27 (40%)	28 (41%)	13 (19%)	14

Summary

1. False incontinence due to irritative lesions of the urethra, vesical neck, and bladder is frequently encountered in women. False incontinence is often confused by the doctor and patient and considered to be stress incontinence. The two conditions may co-exist.

2. No adequate tests have been described to differentiate these two types of incontinence. The so-called continence test cannot be used as a reliable index to measure incontinence.

3. It has been found that dilatation of the urethra, topical applications of silver nitrate, and the use of ephedrine will usually cure false incontinence. The method described may be used, therefore, as a therapeutic test to differentiate false from true stress incontinence prior to surgery.

4. This method may at times be used successfully in preventing unnecessary operations on patients with false incontinence, and in the salvage of patients suffering from incontinence unimproved by surgery; or following operations on the anterior vaginal wall.

5. Of 68 cases of urinary incontinence with adequate therapy and follow-up, 27 (or 40 per cent) were cured; 28 (or 41 per cent) were improved, while 13 (or 19 per cent) were not helped by this form of therapy.

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THE HYDROSTATIC BAG IN OBSTETRICS*

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THE use of the hydrostatic bag in obstetrics has been a debatable point for many years. Opinions expressed in modern textbooks and recent literature lead one to believe that the bag is a relic of a past era, and has no place in modern obstetrics.[1, 3] Others,[2, 4-9] however, maintain that certain indications exist where it may be employed advantageously.

For this reason, it was deemed necessary to collect a series of cases in which the same elastic bag was used and the procedure did not vary. An attempt was made to scrutinize the indications, fetal and maternal mortality and morbidity, along with other complications inherent in the use of the bag. Based on these factors, certain conclusions regarding this controversial subject can be drawn.

Material

The material included in this paper was collected from the obstetric records of the Cincinnati General Hospital. It covered a ten-year period from 1938 to 1947, inclusive. The insertion of the bag and the ultimate delivery were performed by one of the members of the resident staff. Many of these patients were subjected to various vaginal or rectal examinations by members of the house staff and senior medical students for instructional purposes. Others were referred to this hospital following mismanaged labor in the home. Most of them had had no prenatal care. It was expected, therefore, that the maternal morbidity would be high.

Type of Hydrostatic Bag

According to Woodward and Gardner,[9] the earliest bag to be used was a bladder type devised by Schnakenburg in 1831, which was discarded soon thereafter. This was replaced by Carl Braun's rubber balloon-shaped bag. De Ribes and Voorhees described the nonelastic bag, which became popular and is now employed in many hospitals in this country. The nonelastic bag, however, has several disadvantages. When distended with fluid, it acts as a driving wedge, and possesses no elasticity or adaptability. One often resorts to traction to force this unyielding mass through the cervix, frequently with resulting lacerations. Furthermore, different sizes must be used to effect adequate dilatation, necessitating longer time, more manipulation, and greater possibility of infection, trauma, and prolapse of cord.

In this department, the original Braun bag has been modified by technicians† in this city to eliminate all seams and rough edges. (Fig. 1.) It is molded

*Read before the Cincinnati Obstetric Society, Feb. 19, 1948.

†Present bag is made by Mr. Waldo Younkers following the specifications set forth by Dr. William P. Gillespie.

from one piece of natural or synthetic latex, and is pliable enough to vary its contour, depending upon the pressure gradients upon it. The latex bag is made in only one size. It can be introduced readily through a cervix where only 2 cm. of dilatation exist. Quoting from Woodward,[9] "When it (the bag) is placed in the uterus, the pressure upon its upper portion causes that portion within the cervix to expand and to exert outward pressure on the cervical ring in a much more positive manner than the non-elastic, wedge-shaped bag. For this reason, it is only rarely necessary to apply traction . . . When the bag is pushed out by pressure from above, the dilatation is greater than the circumference of the bag, because with each contraction of the uterus the bag is shortened and its circumference expanded."

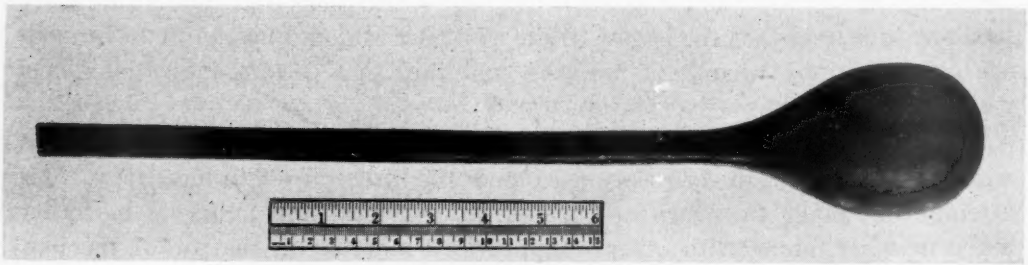

Fig. 1.

Method of Use

The bag is attached by a rubber tubing to a Kelly bottle and sterile water is allowed to run in until the bag is the desired size (usually holding 400 to 500 c.c.). All air is expelled from the bag and tubing. The water is allowed then to run back into the Kelly bottle, creating a vacuum in the bag and facilitating the folding. The collapsed bag is folded and grasped with a curved sponge stick and then is introduced by touch (or preferably by sight) through the cervical os.

When the bag is inside the os, the sponge stick is removed, the tubing unclamped, and the water slowly fills the bag. The neck of the bag is secured with a clamp, and the tubing is disconnected. This technique is preferred to that of filling the bag with a syringe because of its convenience, ease, and less chance for contamination.

Incidence

During the ten-year period included in this paper, there were 22,935 deliveries; in 244 cases the delivery was aided by a bag, giving an incidence of 1 per cent. (Table I.) This rate is higher than that reported elsewhere.[1, 6, 11] The policy of conservative obstetrics has always been dominant in this hospital, and readily accounts for this high incidence. During the last four years, however, the use of the bag has decreased slightly because of the re-evaluation of its indications and the lack of good latex necessary to manufacture new bags.

TABLE I. INCIDENCE OF USE

Total deliveries (1938-1947 inclusive)	22,935
Delivered with bag	244—1%

Indications

Accepting Webster's[6] classification, we schematically divided the patients into three main groups for: (1) Bleeding, (2) aid in cervical dilatation, and (3) induction of labor in toxemia.

Fig. 2 shows the percentage of cases in each group.

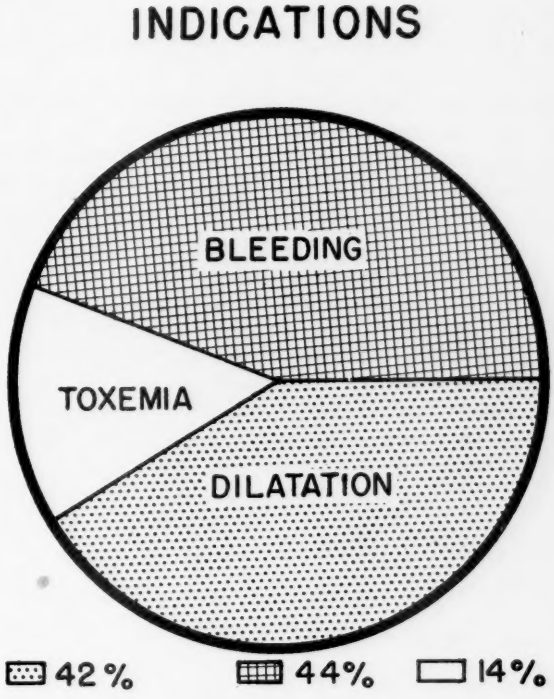

Fig. 2.

(1) Bleeding.—Many authors[4, 6, 7] believe that placenta previa is the major indication for employment of the elastic bag. Table II reveals that this complication accounted for 64 cases. Of these, 12 were central placenta previa; 3 of them were treated by inserting the bag in the vagina in an attempt to control hemorrhage until the operating room could be prepared for cesarean section. In these 3 cases the infants survived, while 7 of the remaining 9 cases delivered vaginally resulted fatally for the infants. Therefore, we no longer advise the bag in the treatment of central placenta previa. The present trend of thought in this department is to limit the bag to partial placenta previa (with artificial rupture of the membranes) when the cervix is soft and partly dilated. The marginal type is treated most advantageously by rupture of the membranes alone, and, occasionally, by bag insertion.[10] In the majority of cases of placenta previa, the infant is premature and can be delivered easily by the vaginal route, following control of hemorrhage and cervical dilatation.

Abruptio placentae was the second indication among the bleeding patients. The bag was used 23 times for this complication, and only three live infants were delivered. The majority had no fetal heartbeat on admission.

Abruptio placentae in the multipara is still listed among our primary indications. This is justified by the fact that the infant has usually expired

in utero when the diagnosis is made, and the cervix often is partially dilated, soft, and easily amenable to vaginal delivery. In the primipara with a long, hard, uneffaced cervix, the procedure of choice is cesarean section regardless of whether the infant is alive or dead. In abruptio placentae as well as in other types of hemorrhage, the membranes were ruptured artificially first, bringing about as much contraction of the uterus as possible, and the bag inserted intraovularly. It is necessary also to note exactly when the bag is expelled from the uterus in order to prevent the accumulation of blood behind it. As soon as the bag is found in the vagina, the patient should be prepared for immediate delivery.

The same criteria have been applied to partial separation of the placenta. Seven cases of this type having been treated with the bag, resulting in five living, one stillborn, and one nonviable infant. Other types of bleeding, listed in Table II, are of secondary importance and need no further discussion.

TABLE II. INDICATIONS FOR USE

INDICATION		NO. OF CASES
1. *Bleeding.*—		
A. Placenta Previa		64
Central	12	
Partial	29	
Marginal	23	
B. Abruptio placentae		23
C. Partial separation		7
D. Late abortion		4
E. Circumvallate placenta		2
F. Low Implantation		5
G. Undetermined		3
Total		108
2. *Dilatation.*—		
A. Prolonged labor		54
B. Breech		19
C. Transverse		13
D. Twins		4
E. Miscellaneous		12
Total		102
3. *Toxemia.*—		
A. Pre-eclampsia		20
B. Eclampsia		14
Total		34

(2) Dilatation.—In this group were included the patients in whom the bag was used to secure full cervical dilatation because of insufficient natural forces, or because of some abnormality in presentation. The presence of the bag in the lower segment and cervix initiated regular contractions, and dilatation proceeded rapidly. The bag was chosen only after elimination of cephalopelvic disproportion as an etiological factor. Accordingly, 54 cases classified as prolonged labor, due either to uterine inertia or cervical dystocia, were delivered after being aided by the elastic bag. (Table II.) Adequate cervical dilatation was successfully secured in all cases.

Breech, mostly footling variety, and transverse presentations constituted other indications. Reduction in fetal mortality was secured in the cases of transverse presentation treated by the use of the bag. The reason for this was that the bag not only secured cervical dilatation, but prevented rupture of the membranes and prolapse of the cord, thereby facilitating the performance of delivery by podalic version.

Other cases (miscellaneous) of premature rupture of the membranes, prolapsed cord, twins, brow presentation, face presentation, anencephalics, also were treated with the bag.

(3) Toxemia.—It is well recognized that the best approach in the treatment of patients with toxemia is along conservative lines. The policy of this department has been to induce labor in eclamptics only after the convulsive stage has been controlled, and the patient is in good general condition. Medical induction with stripping of the membranes is attempted first. Where this fails, and when the condition of the cervix permits, a bag is inserted extraovularly, and delivery is effected by the vaginal route. In rare cases, because of disproportion, or the condition of the cervix, cesarean section is performed.

Induction of labor was secured by the bag in 20 pre-eclamptic and 14 eclamptic patients. (Table II.) Eighteen living babies were delivered, giving a gross fetal mortality of 48 per cent and corrected of 30 per cent.

Type of Delivery

In this series there were nine sets of twins, giving a total of 253 infants. Spontaneous and podalic version were the predominant types of delivery. (Table III.) Five patients were delivered by cesarean section after the insertion of the bag. As stated before, in three cases of central placenta previa the bag was used in the vagina to control hemorrhage. In the remaining two, cephalopelvic disproportion was not detected, and extraperitoneal cesarean section was performed after an unsuccessful attempt to perform vaginal delivery.

TABLE III. TYPE OF DELIVERY

	NO. OF CASES	SPONTANEOUS	PODALIC VERSION	FORCEPS	BREECH	CESAREAN SECTION
Bleeding	108	54	34	7	10	3
Dilatation	102	18	28	27	27	2
Toxemia	34	15	8	6	5	0
Total	244	87	70	40	42	5

Parity

Table IV shows that, in the bleeding cases, 85 per cent were multiparas, mainly because placenta previa was more common in the multiparas, and most of the primiparas were treated by cesarean section. Of the total, 66 per cent were multiparas.

TABLE IV. PARITY

INDICATION	PRIMIPARAS	MULTIPARAS
Bleeding	16	92
Dilatation	52	50
Toxemia	15	19

Complications

Puerperal infection frequently follows the use of the hydrostatic bag.[2, 3, 11] Many authors have decided to eliminate its employment chiefly because of this danger. With this in mind, careful study was made of all cases which presented a temperature of 100.4° F. on any two days, exclusive of the first twenty-four hours post partum. Eighty-six patients were classified as infected.

(Table V.) Fig. 3 shows the incidence of morbidity in each group of cases. In the bleeding group, the morbidity was higher because some of the patients were in poor general condition upon arrival at the hospital, due to extreme blood loss. Recently, we have been able to lower the maternal morbidity considerably with prophylactic sulfonamides, and parenteral or vaginal penicillin.[12]

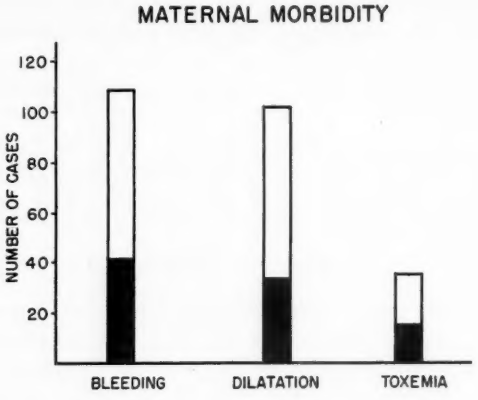

Fig. 3.

TABLE V. COMPLICATIONS

	CASES	PER CENT OF TOTAL
Infection	86	35
Cervical laceration	9	3.7
Prolapsed cord	24	9.8

Nine cases were found to have cervical lacerations. The trauma, however, was possibly produced by the internal podalic version which frequently followed the extrusion of the bag.

Prolapse of the cord occurred in 24 cases resulting in six infant deaths and three nonviable stillborns. These figures might possibly be reduced by more careful auscultation of the fetal heart immediately after insertion of the bag, and again after its expulsion into the vagina.

Displacement of the fetal position is attributed by several authors to the use of the bag. This complication, however, was observed only in a few cases, and did not cause serious difficulty in the outcome of the delivery.

Fetal Mortality

The gross fetal mortality for the entire series was 43 per cent and the corrected 25 per cent. (Table VI.)

Fig. 4 shows the corrected fetal mortality in each group. These figures were corrected by excluding congenital abnormalities incompatible with life, and macerated, nonviable fetuses. Prematurity was not considered as a correction factor. For the bleeding cases, the corrected fetal mortality dropped from 57 to 27 per cent; for the dilatation group, from 27 to 20 per cent; and for the toxic group, from 48 to 30 per cent. Our gross fetal mortality was less than that reported by Webster,[6] but our corrected mortality was apparently higher, because of a difference in the correction factor.

TABLE VI. FETAL MORTALITY

	NO. OF CASES	STILLBORN	NEONATAL DEATHS	TOTAL	GROSS MORTALITY RATE (PER CENT)
Dilatation	108	54	7	61	57
Bleeding	102	22	6	28	27
Toxemia	34	12	4	16	48
Total	244	88	17	105	43

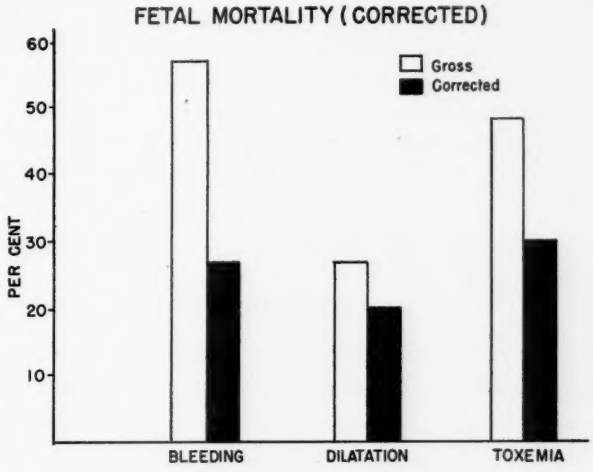

Fig. 4.

Prematurity

Eighty-seven infants were premature, and 52 of these were either stillborn, or died neonatally. (Table VII.) The highest incidence of prematurity was observed in the bleeding cases. These figures emphasize the fact that the use of the bag is a wise procedure in a patient with a premature infant having only a minimal chance of survival. Premature babies were classified according to their weight (less than 2,500 Gm.), and according to the length of gestation.

TABLE VII. PREMATURITY

	CASES	PREMATURES	DEATHS	PREMATURE MORTALITY RATES (PER CENT)
Bleeding	108	54	38	70
Dilatation	102	13	7	53
Toxemia	34	20	7	35
Total	244	87	52	60

Maternal Mortality

There were four maternal deaths in this series. In none of these, however, could a definite relationship between the cause of death and the use of the bag be demonstrated.

The first case was a 42-year-old multipara, admitted to the hospital because of antepartum eclampsia, bronchial asthma, and heart failure. She was delivered by an internal podalic version and breech extraction following bag induction. She developed a subphrenic abscess, and died 35 days after admission.

The second case was a 35-year-old, colored multipara admitted in shock with a diagnosis of placenta previa marginalis. She was delivered by internal podalic version after insertion of the bag. Death was due to uncontrolled hemorrhage, and autopsy revealed a laceration of the lower uterine segment, which was not recognized and possibly was due to the mode of delivery.

The third case was a 32-year-old, white multipara admitted in severe shock, with a diagnosis of premature separation of a low implanted placenta. Delivery was by podalic version and breech extraction after insertion of the bag. She died of infection a month later.

The fourth case was a 32-year-old, white multipara who presented the findings of the dystocia dystrophy syndrome with primary uterine inertia. Dilatation was secured with the bag, and she was delivered by internal podalic version and breech extraction. Severe postpartum hemorrhage ensued, and a delayed hysterectomy was performed, but the patient died a few hours later.

In all of the aforementioned cases, death was considered preventable.

Discussion

An analysis of the figures reported in this paper leads one to believe that there is still a place for the hydrostatic bag in obstetrics. The success of this procedure, however, depends on several factors: the choice of the type of bag to be used, the technique of its employment, the judicious selection of cases, and the close observation of the patient during labor and delivery. The selection of the correct bag and the type of patient are of paramount importance.

The fetal mortality in this series could not be compared with that reported for cesarean section since many of these patients were not suitable for abdominal delivery.

The maternal morbidity could be reduced by regular use of antibiotic drugs. Furthermore, the use of the bag in such cases was justified by the large incidence of prematurity and multiparity, and by the poor general condition of the patients.

From the available data, the following indications for the use of the hydrostatic bag can be selected:

1. Placenta previa partialis, and occasionally marginalis.
2. Abruptio placentae when the infant has already expired, and the cervix is somewhat dilated and soft.
3. Transverse presentations in the multipara when the cervix is amenable.
4. Breech presentations, particularly footling variety in the primipara, or in the multipara with partially obliterated cervix, and when there has been premature rupture of the membranes and failure to progress.
5. Induction of labor in the toxemic patient when the cervix is amenable, and more conservative methods have failed.
6. Uterine inertia in the absence of disproportion, when there is no evidence of intrauterine infection.

Summary

Two hundred and forty-four patients delivered with the use of a hydrostatic bag were studied.

A type of bag made of latex, the technique, and the advantages of its use were described.

Control of bleeding, induction of labor, and securing cervical dilatation were the major indications for the use of the bag.

The gross fetal mortality was 43 per cent, and the corrected (including prematures) 25 per cent.

The maternal death rate in this series was 1.7 per cent.

Infection and prolapse of cord were the major complications.

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CHONDRODYSTROPHY FETALIS

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INTEREST in the subject of chondrodystrophic dwarfism was given added impetus at The Chicago Lying-in Hospital, when, on April 22, 1947, a chondrodystrophic infant was delivered by cesarean section. Both parents of this baby were typical chondrodystrophic dwarfs. Although the incidence of infants born with this developmental defect is not sufficiently rare to warrant comment, the fact that both parents also presented this form of dwarfism makes the case worthy of report and some discussion. The very extensive work of Rischbieth and Barrington[1] (1912) lists only two instances in which a baby and both parents were chondrodystrophic. A partial review of the literature from 1901 to 1942 discloses no similar cases. A newspaper item published in Denver, Colorado, in 1943, stated that a dwarf baby had been born by cesarean section to dwarf parents, but we have been unable to verify this report. Both parents seem to have been dwarfs, but whether they were chondrodystrophic is not certain.

Our case report is as follows:

Mrs. J. M., a 28-year-old white, primigravid, married, chondrodystrophic woman, first reported to The Chicago Lying-in Outpatient Department on November 29, 1946, for prenatal care. She was escorted by her husband, who was also a typical chondrodystrophic dwarf. Her past medical history was not noteworthy except that she had had defective skeletal development since birth. She had attended public schools, where her progress had been average. The patient's father and mother are living, well and normal. She has five sisters and one brother, all living, well and normal. No dwarfism was found when her pedigree was traced through four generations. The patient's husband was able to establish a pedigree through three generations in which there was no dwarfism. His father, mother, and three brothers are all living, well and normal. Each of his brothers is married and has two, three, and three normal children, respectively. Mrs. J. M.'s obstetric history was not unusual. Her menses appeared at the age of 15 years, the cycle was twenty-eight days, and the duration was two days. Her last menstrual period was August 20, 1946, and it was normal. The estimated date of confinement was May 27, 1947. Physical examination showed the patient to be in good health. All the findings characteristic of chondrodystrophy were present. There was no evidence of rickets. Her height was 116 cm., and she weighed 33.7 kg. The pelvic examination was recorded as follows: external genitalia normal; introitus nulliparous; vagina normal; the cervix was above the pelvic inlet and could not be palpated because of the pelvic deformity; the sacrum was displaced anteriorly so as to lie almost against the symphysis; the uterus, palpated abdominally, was enlarged to the size compatible with twelve weeks' gestation; the adnexae could barely be reached through the lateral portions of the pelvis and no abnormalities could be made out; a moderate lumbar lordosis was present. The pelvic measurements were: intercristal 21 cm.; interspinous 20 cm.; bitrochanteric 27 cm.; external conjugate 13 cm.; biischial 6 cm.; the pubic arch was narrow and the angle at the symphysis was acute; the conjugata vera was no more than 2 cm. The patient was given routine prenatal care, and it was anticipated that pregnancy would be terminated by laparotrachelotomy at approximately the 38th week of gestation.

The prenatal course was uneventful until April 22, 1947, at which time active labor began and the membranes ruptured spontaneously. A cesarean section was performed immediately, using ½ per cent Novocain local anesthesia. A living, female, premature chon-

drodystrophic infant was delivered. She cried spontaneously and appeared to be in good condition. The mother's postoperative course was normal and she was discharged on the twelfth hospital day.

The infant at birth weighed 2,310 Gm., measured 43 cm. in total length, and was of 34 weeks' menstrual age. Physical examination revealed the following characteristic findings of chondrodystrophy: mild macrocephaly, prominent frontal and parietal bosses, saddle-pug nose, abnormal shortness of the extremities associated with exaggerated curvature of the long bones and overgrowth of soft tissue, trident-shaped hands, and normal length of the body trunk. The infant's hospital course was not unusual except that weight gain was slow. The baby was discharged on the twenty-first hospital day weighing 2,510 Gm. (Fig. 1). Subsequent examination on July 3, 1947, revealed a well, vigorous infant who was gaining weight normally.

Fig. 1.

Discussion

The management of this case presents no obstetric problem. The indication for cesarean section in all chondrodystrophic dwarfs is clear cut and without alternative. As

was recognized by Rischbieth and Barrington in 1912, no chondrodystrophic woman can deliver a viable baby vaginally because of the pelvic deformity constantly associated with this condition.

In spite of the great interest in dwarfism, as evidenced by the accumulated historical records, literary classics, objects of art, and scientific reports, the etiology of chondrodystrophic dwarfism remains vague and subject to debate. The malformation has been attributed to almost every possible cause. At the present time it is generally believed that heredity is an important factor and that mutations producing this abnormality and subsequently capable of being inherited appear with a fair degree of frequency. It is not clear whether the hereditary effect is transmitted through the endocrine system or through the factors concerned with skeletal development. That the hereditary aspect of dwarfism is not a recent idea is evidenced by the attempts of Catherine de Medici and others to produce a dwarf race by intermarriage. Study of pedigrees in which chondrodystrophy occurs leaves no doubt that heredity is involved. Geneticists in general are of the opinion that the inheritance is transmitted through simple Mendelian factors. The failure of dwarfism to appear in all generations of a pedigree is explained by the so-called "skipping mechanism" due to a lack of "penetrance" of the genes.[2]

Related to the hereditary aspects of chondrodystrophy is the high death rate of affected babies. The high incidence of intrauterine death at about the eighth month of gestation is recognized, and the prognosis for those babies born alive must always be guarded since many die during the first year of life. No satisfactory explanation has been advanced for this high mortality, although it has been suggested that, in many instances, early death is due to a premature synostosis of the four segments of the occipital bone, resulting in a compression of the growing spine and brain stem at the foramen magnum. The "lethal effect" of homozygous inheritance factors has been suggested as a cause of early death and has been supported by proof of this phenomenon in experimentation with chondrodystrophic animals.

Since 1931, during the course of over 48,000 deliveries, four other chondrodystrophic infants have been born at The Chicago Lying-in Hospital. Two were delivered by cesarean section, one by version and extraction, and one by midforceps. None of these babies survived; all were stillborn or failed to live beyond the early neonatal period. Six other chondrodystrophic infants were received at this hospital for autopsy from other Chicago sources. The parents of all ten infants were without evidence of chondrodystrophy and in no instance could a history of dwarfism in other members of the family be obtained.

During the period of Mrs. J. M.'s hospitalization, it was possible to contact eleven other chondrodystrophic dwarfs in the Chicago area. These people were all willing to discuss their deformity. The following information and opinions were obtained from them:

1. The estimated number of chondrodystrophic dwarfs in the Chicago area is forty.
2. The estimated number of chondrodystrophic dwarfs in the United States is approximately 2,000. (No accurate census is available.)
3. The parents of the 11 individuals interviewed were normal, and there was no other dwarfism in their families.
4. The individuals contacted knew of the following families in which dwarfism is present:
   a. Four families in which the father is chondrodystrophic and the mother is normal. The children of these parents are all normal.
   b. One family in which husband, wife and three children are normal and three children are chondrodystrophic.
   c. One family in which both husband and wife are normal but all of their five children are chondrodystrophic.
5. Very few chondrodystrophic dwarfs marry. Those who do usually marry normal individuals. Marriages in which husband and wife are both chondrodystrophic are exceedingly rare.

Conclusions

1. Two instances have been found in the literature in which father, mother and child are chondrodystrophic dwarfs. The present report brings the total to three.

2. Cesarean section is always indicated for the delivery of a pregnant chondrodystrophic woman.

3. Prognosis for survival of chondrodystrophic infants should be guarded.

4. Chondrodystrophic children, for the most part, appear in families in which both father and mother are normal.

5. Chondrodystrophy seems to be inherited as a simple, dominant, Mendelian character complicated by:

   a. Mutations which occur more frequently than has been generally appreciated.

   b. "Skipping phenomenon."

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TORSION OF FALLOPIAN TUBE

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TORSION of a tube is not a rare condition, but torsion of a previously undiseased tube is. Regad,[1] in discussing the relative frequency of torsion of the tube based on 201 cases, found torsion of the undiseased tube in 24 per cent of the cases. However, histologic examination was done in only 8 per cent of these. It is my belief that, had it been done in more of these, there would have been found a smaller percentage of previously undiseased tubes. He found torsion of a hydrosalpinx in 18 per cent, torsion in hernial sac in 14 per cent, torsion in salpingitis, ectopic, or tumor in 13.5 per cent; torsion in the course of pregnancy in 12 per cent, with various other conditions making up the additional percentage. Anderson[2] reports the torsion of an apparently normal ovary and spontaneous amputation of the tube occurring in a 12-year-old girl with a one-day history of pain. In this case the tube was amputated 1.5 cm. from the cornu. Kaminester[3] reported the case of a 24-year-old patient; gravida i, para i, with a twist due to a small parovarian cyst. Goldberg and Olim[4] reported a case due to twisted hydrosalpinx. Savage[5] reported a case of a twisted hematosalpinx complicating pregnancy. That case was the fifteenth reported up to that time.

The case to be reported here is that of a torsion of a previously undiseased tube.

Case History

Mrs. J. M., a 37-year-old gravida ii, para ii, was admitted to the South Nassau Communities Hospital complaining of pain in the right lower quadrant of three days' duration. Patient's periods began at 15½ years and were always regular until last pregnancy. Since then she has on several occasions been as much as two days late. Patient had a normal period in April, 1947. Her May period, however, was five days late, occurring on May 30, and being normal in amount and duration. The evening of June 15, she developed pain in lower abdomen particularly on the right side. The pain became severe during the night. Findings were: normal pulse and temperature, a soft abdomen, with slight tenderness in the right lower quadrant. A white blood cell count and differential count done the next day were normal. Patient, however, continued to have intermittent pain in the lower abdomen on June 16 and 17. Early on the morning of the 18th, she had more severe pain and while in the bathroom actually fainted.

At this time she was seen in consultation, and the significant findings were a temperature of 100° F., pulse 100. The abdomen showed definite spasm and rigidity of the lower quadrants, particularly on the right side. There was direct tenderness in the right lower quadrant but even more marked rebound tenderness. External genitals were normal; cervix not particularly soft; fundus of normal size and firm. In the right fornix was a mass measuring about 6 by 8 cm. This was exquisitely tender and felt cystic. There was no blood on the examining finger. With these findings, patient was admitted to hospital with a diagnosis of either a right ectopic pregnancy, with tubal abortion, or, a twisted right ovarian cyst.

Laboratory Data: The red blood count was 4.1 million, hemoglobin 82 per cent, white blood count 9,000 with 80 per cent polymorphonuclear leucocytes. The urine was negative.

Patient was operated upon shortly after admission to the hospital. Upon opening the peritoneal cavity, it was noted that there was an increased amount of fluid, culture of which was taken, and subsequently found to be sterile. There was no blood in the peritoneal cavity. The only pathologic finding was that in the right tube. This showed two complete twists upon itself at the midportion. The proximal portion of the tube appeared normal. The distal half, however, was much dilated measuring 6 by 8 cm. The fimbriated end was closed. The dilated portion of the tube was tense, cystic, and showed bluish-red discoloration. A right salpingectomy was done.

Pathologic Report.—Specimen consists of a tube, the proximal portion of which appears normal. The distal half is dilated, measuring 6 by 8 cm. The fimbriated end is closed. Section of the dilated portion of the tube reveals the presence of serosanguineous fluid. There is also some clotted blood present in the lumen and wall of the tube.

Diagnosis.—Twisted hematosalpinx.

Patient had an uneventful convalescence. The wound healed by primary union and the patient was discharged on the eighth postoperative day.

Comment

The case presented is one of torsion in a previously undiseased tube. This is corroborated by the finding of normal tubal lining and diameter in the portion of the tube proximal to the twist. The normal appearance of the other tube, plus the fact that the patient has two young children, likewise point to a conclusion that the tube was normal prior to the present episode. The exact frequency of occurrence of this condition in a nondiseased tube is difficult to determine because the pathologic examination is frequently inaccurate, the marked necrosis usually present obscuring the rest of the picture.

Blum and Sayre,[6] in their article, review the various theories as to the possible mechanism of this condition. Of the various theories postulated, the following impressed me as being the most likely:

1. Anatomic theory, which states that malformations in the mesosalpinx or the tube favor torsion, e.g., long mesosalpinx, hydatids of Morgagni, persistence of the spiral winding normally present in the tube of the fetus.
2. Physiologic theory that a disturbance of the regular peristaltic movements of the tube, such as spasm, may give this condition.
3. Hemodynamic. The veins of the mesosalpinx are longer and more flexible than the arteries, and, in case of venous congestion, they assume a spiral course which favors torsion.
4. Sellheim's theory that sudden changes or stoppage of body movement may give rise to torsion.

The reason for the occurrence of this condition in the present case must remain unknown. There was nothing in the patient's previous history or in the operative findings to account for the occurrence of this condition.

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USE OF ESTINYL IN TREATMENT OF MISSED ABORTION*

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WHEN a growing fetus dies, it becomes in effect an intrauterine foreign body, which is usually expelled within a short time thereafter. Occasionally the entire dead material is retained within the uterine cavity for long periods before expulsion. There have been reports of instances where this situation continued for almost a year. The condition of dead and completely retained fetal mass has been named "missed abortion."

The evacuation of the products of conception in cases of missed abortion has long been a problem. In many instances the uterus seems to lack its normal capacity for contraction, and the emptying of the uterine contents is delayed until an operative procedure is performed for that purpose. Any agent that increases uterine irritability and contractility is therefore of distinct advantage. The use of estrogens which might increase uterine response would therefore seem rational under these circumstances.

By replacing the hydrogen at carbon atom 17 in alpha-estradiol with the ethinyl radical, a remarkable increase in effectiveness results. The product thus produced is ethinyl estradiol, hereinafter referred to as Estinyl. On a weight basis, Estinyl is from seven to seventy-eight times as active as other oral estrogens available today. Absorption is virtually complete in the gastrointestinal tract, and the ethinyl radical prevents inactivation of the estrogen by the liver. In regard to toxicity, 10 to 20 per cent of all nonpregnant patients experience gastrointestinal and other symptoms. The complaints referred to the digestive system are nausea and, more uncommonly, vomiting, diarrhea, and abdominal pain. Vertigo and headache have been reported. In pregnant patients, we have seen no untoward effects, though occasionally the tablets of Estinyl are excreted in the stool within half an hour or an hour after ingestion, intact and undigested.

Six cases of missed abortion are described which were treated by the administration of large doses of Estinyl with favorable results.

CASE 1.—D. C., aged 29 years, was admitted to the hospital on Sept. 24, 1945, because of vaginal bleeding of fours days' duration. She had had two previous pregnancies, both full term, with spontaneous deliveries. Her last menstrual period was March 10, and the expected date of confinement was December 17. The patient stated that her abdomen seemed larger three months prior to admission than at the present time. On September 25, colostrum could be expressed from the breasts, but no milk. Abdominal examination revealed a rounded mass reaching to the umbilicus, about the size of four and one-half to five months' gestation. This ovoid swelling was definitely the uterus, as contractions and relaxations could be palpated. No fetal heart or movements were heard; there was no choc fetale. On vaginal examination, the cervix was soft with the external os open, but the internal os was closed and firm. A diagnosis of missed abortion was made. The Aschheim-Zondek test was negative of September 28. Radiologic examination of the abdomen revealed a pregnancy of about four and one-half months.

*We wish to thank the Schering Corporation for their generous supplies of Estinyl which made our study possible.

On September 29 at 9:00 A.M., 0.3 mg. of Estinyl was administered by mouth. Uterine cramps began three hours later, and the medication was continued at four-hour intervals. After 0.9 mg. of Estinyl had been given, good labor began. The membranes ruptured at 8:15 P.M., and a spontaneous delivery of a macerated four months fetus was accomplished. The placenta was expressed but it was not entirely intact, and digital curettage of the uterine cavity was performed. A small amount of placenta was obtained thereby. The postpartum course was uneventful, and the patient was discharged on Oct. 6, 1945.

CASE 2.—H. L., aged 32 years, was admitted on Sept. 20, 1945. She had had one previous pregnancy which was terminated by a low forceps delivery at full term. Her last menstrual period was April 19, and the expected date of confinement was January 26. On July 18 a third degree retroversion of the uterus was corrected by bimanual manipulation. On August 26 vaginal staining began and continued intermittently until the time of admission to the hospital. At no time was bleeding excessive, and there were intervals of several days to a week without any stain of bleeding. On August 30 the uterus was the size of a three and one-half months' gestation. On September 10 the Aschheim-Zondek test was positive. On September 19 a vaginal examination was performed because the uterus could no longer be palpated above the symphysis. The uterus was now the size of a ten weeks' gestation, soft and doughy in consistency. There was a slight bloody discharge. The diagnosis of missed abortion was made.

On September 20 at 9:00 A.M., 0.3 mg. of Estinyl was administered by mouth, and repeated every four hours until 0.9 mg. had been taken by the patient. Uterine contractions began soon after the third dose when the patient went into active labor. Within four hours spontaneous delivery of an abnormal ten weeks fetus occurred. The baby showed webbing with lack of development of the fingers and toes. The placenta was expressed, but this was not complete. A curettage was necessary to remove the remaining secundines. The placenta was thin and poorly nourished. Her postoperative course was uneventful, and the patient was discharged on September 23. On October 17 vaginal examination revealed the cervix closed and normal. The uterus was retroverted and slightly smaller than normal.

CASE 3.—B. L., aged 24 years, had her last menstrual period on March 6; this was her first pregnancy. She began to bleed on May 21, and a diagnosis of threatened abortion was made, and hormone therapy begun. The patient was examined on June 6, and the uterus found to be the size of a seven weeks' gestation. A diagnosis of missed abortion was made, and Estinyl 0.3 mg. was administered by mouth every two hours. After four doses—a total of 1.2 mg.—the patient expelled the complete sac, containing the placenta. No fetus was found. Her postpartum course was uneventful. The patient was checked over six months later as to capabilities for carrying a pregnancy to successful termination; endometrial biopsy showed a very poor progestational phase premenstrually. This patient is now just over three months pregnant, and on therapy outlined in a previous paper. This young woman is one of three married sisters, of whom one has two children, and the other miscarried twice, finally being carried to term with the third pregnancy on considerable hormone therapy.

CASE 4.—Mrs. T. was admitted to the hospital with a diagnosis of missed abortion. The last menstrual period had occurred six months previously. The uterus was the size of a four months' pregnancy. No fetal movements were heard, and the fetal heart was absent. Estinyl 0.3 mg. was given every two hours for six doses per day, over a period of four days, the total amount of Estinyl being 3.0 mg. On the fourth day, the patient went into good labor, and delivered spontaneously a complete sac, with macerated fetus and placenta; the fetus had three loops of cord wound tightly around the neck.

CASE 5.—R. S., aged 22 years, was admitted to the hospital on Oct. 15, 1946. This was her third pregnancy, the two previous being entirely normal. The last menstrual period was March 24, 1946. No fetal heart had been heard, and a diagnosis of fetal death had

been made at five months, and confirmed on admission by x-ray. No labor pains occurred during five days, and 0.3 mg. Estinyl was ordered every two hours. The patient went into active labor after nine doses of Estinyl, the total dose being 2.7 mg. A macerated stillborn fetus was delivered after two and one-half hours.

CASE 6.—B. S., aged 28 years, was admitted with a diagnosis of missed abortion. Her last menstrual period had taken place eight months previously, and no fetal movements had been felt since five and one-half months. No fetal heart was audible. Estinyl 0.3 mg. was administered every two hours for 41 doses, total amount being 12.3 milligrams. The patient did not go into labor, even though the Estinyl had been given for seventy-two hours, and Methergine one minim was given every thirty minutes, for three doses, producing strong tetanic uterine contractions, which lasted several minutes. The drug was stopped and the pains subsided. Methergine was again started, and strong contractions, though not tetanic, were elicited. The patient went into good labor and was delivered of a macerated fetus, the size of a five months' pregnancy. The use of Methergine is still under study by us. It is our belief that the Estinyl sensitized the uterus to the action of Methergine, resulting in the tetanic contractions.

Conclusions

Evacuation of the products of conception in cases of missed abortion was attempted by the administration of Estinyl. Results were generally very good, in five of six cases so treated. The dosage used was usually 0.3 mg. every two hours for a period of seventy-two hours if necessary. There were no untoward effects.

Since treatment of these cases, larger doses of Estinyl have become available to us for research. An article by us, on the induction of labor at term by the administration of Estinyl, is now in print. In those studies, it became apparent that larger, much larger, doses of Estinyl could and should be used; and it is now our practice to use as much as 1 mg. per dose, every hour. We feel that a result should be expected within, or at approximately, seventy-two hours, and that the medication should be continued for that period if necessary.

Our studies and results with Estinyl indicate that it is a potent estrogen, capable of initiating and maintaining labor contractions in the pregnant uterus. It is of considerable value in the treatment of missed abortion.

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969 PARK AVENUE

CONJOINED FETUSES (THORACOPAGUS) IN A DIZYGOTIC TRIPLET PREGNANCY

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MULTIPLE births, especially those involving more than two off-spring, never fail to arouse considerable interest. If some unusual feature accompanies the multiple births, interest is correspondingly increased.

The present case consisted of a female and two conjoined (thoracopagus) males. This seems to be the first case on record in which conjoined males have complicated a triplet pregnancy.

A noteworthy distinction of these conjoined fetuses is that the umbilical cord contained blood vessels normal for a single individual, i.e., two arteries and a vein. Messenger and Shryock reported a similar case from our own laboratory a few years previously, but their specimen had two arteries and two veins, one of each going to each twin. Shaw, Brumbaugh, and Novey reported conjoined twins with six blood vessels in the umbilical cord which was a matter of simple duplication.

Clinical History and Delivery.—The mother was a primipara, twenty-three years of age. The father was twenty. There was no history of multiple births in either family. Wassermann reports were negative at the time of the marriage in August, 1945. The last menstruation was slight, lasting for but one and one-half days, and began Dec. 26, 1945.

The mother appeared to be in excellent health. There was no history of illness or injury during pregnancy. There was no evidence of vitamin or nutritional deficiency. There was no history of alcoholism, exposure to radiations, or the use of chemical douches or contraceptives. The mother worked until two weeks before the time of delivery. Her gain in weight was from 140 to 169 pounds.

The mother had been employed at the Corona Hospital, Corona, Calif. Delivery took place in this hospital. The first stage of labor began at 10:00 A.M., July 15. The membranes ruptured at 2:18 A.M., July 16. A female was born at 2:28. Birth was described as "easy," the child having "shot out like a cannon ball."

After this, the cord was clamped on the placenta side, there being no effort made to express the placenta as it was evident that another fetus was in the uterus. All pains ceased. At 4:00 A.M., pains began again but were very mild. One-half c.c. of Pituitrin was given. At 4:05, three feet, two rights and a left, appeared at the vulva. Examination was made to determine to which individual the right and left ones belonged. Attempts were made to reintroduce the other right one into the uterus. Traction was made on the left and right feet of one individual until they protruded outside the birth canal. The reintroduction of the foot and leg of the other individual into the uterus was unsuccessful. Further traction on the partially born individual was likewise unsuccessful. At this time, evidences of viability ceased. After consultation it was decided to extract first one and then the other. All attempts to do this were unsuccessful. Traction was increased to maximum until the abdominal wall of one individual ruptured. The twins were finally born en masse at 5:40 A.M.

Cervical and peritoneal repairs were made and the mother made an uneventful recovery.

The female, born first, was placed in an incubator but died at 1:46 P.M., July 16. Her weight was 3 pounds, 1 ounce. The combined weight of the twins was 5 pounds, 8 ounces. Crown-heel length indicated an approximate age of seven months.

Unfortunately, the fetal membranes were not preserved, but the attending physician had observed that there were two placentas, two umbilical cords, two amnions, and two chorions. One of each of these belonged to the female and the other to the conjoined males.

Fig. 2.

Fig. 1.

Fig. 1.—Seven-month conjoined males. Note ruptured abdomen of fetus Two.
Fig. 2.—Radiogram of twins.

Gross Observations and Dissection.—For convenience the twins were numbered. The uninjured one was called "One." Superficially it appeared to be a little the larger.

There was a common uncalcified sternum. The two were joined from about the second rib to a point one-half inch below the diaphragm. The cavities and organs were partly common and partly paired. A common diaphragm separated thoracic regions from the common abdomen. The bodies were not exactly opposite but were slightly offset from the midline laterally.

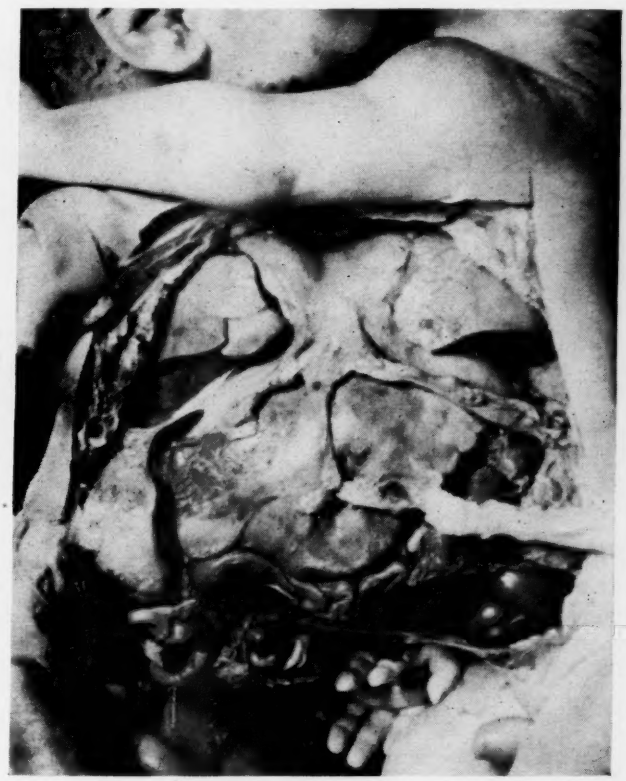

Fig. 3.—Internal organs.

An examination of the umbilical cord showed but three blood vessels, two arteries and a vein. The umbilical cord joined the abdomen at the midline between the two, but both arteries led to fetus Two. The vein led to the common liver.

The large common liver received the umbilical vein on the side of fetus Two. This was traced through the ductus venosus until it joined with the hepatic vein on the same side. A smaller hepatic vein arose from the capillary bed of the liver on the other side and led to the common heart on the side of fetus One. (See Fig. 3.)

Two gall bladders were found. A well-developed one was found between liver lobes on the side of fetus Two and an imperfect one on the other side.

The lungs, esophagus, stomachs, kidneys and spleens were double and appeared normal. The thymus of Two was larger than in One.

Just below the stomachs, there was a fusion of the intestine into one tract. The duodenum of One entered that of Two. Number Two seemed definitely to have the principal tract. The intestine continued as one until an enlargement was formed and the ileum divided. There was more meconium in the large intestine of One than of Two. Anal openings were normal. The appendices of each measured 2.6 cm. (See Fig. 4.)

The heart presented two well-formed atria, a large "left" ventricle on the side of fetus One and a small "right" ventricle on the other side. The foramen ovale was observed.

Both atria emptied into the large ventricle. Ascending aortae arose from opposite sides of this ventricle, one to each fetus. A patent interventricular foramen joined the two ventricles. A pulmonary artery ran from the small ventricle and branched presently to the lungs of each fetus. A ductus arteriosus joined the pulmonary artery in fetus Two with its aorta. Both atria received pulmonary veins and superior venae cavae in addition to the inferior ones mentioned previously.

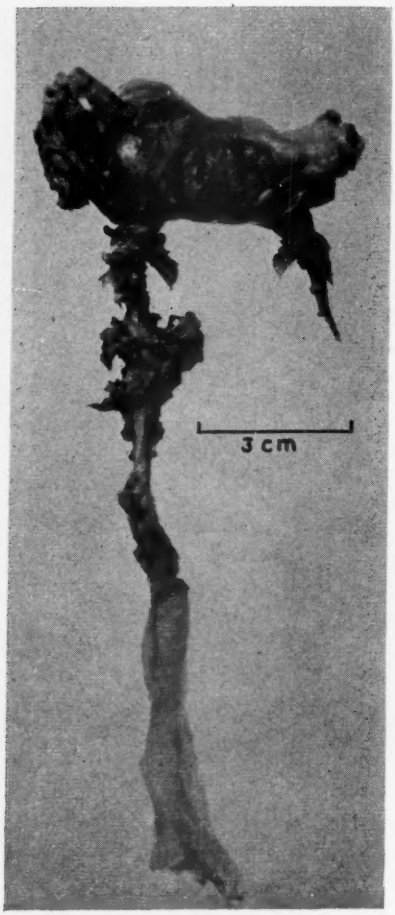

Fig. 4.

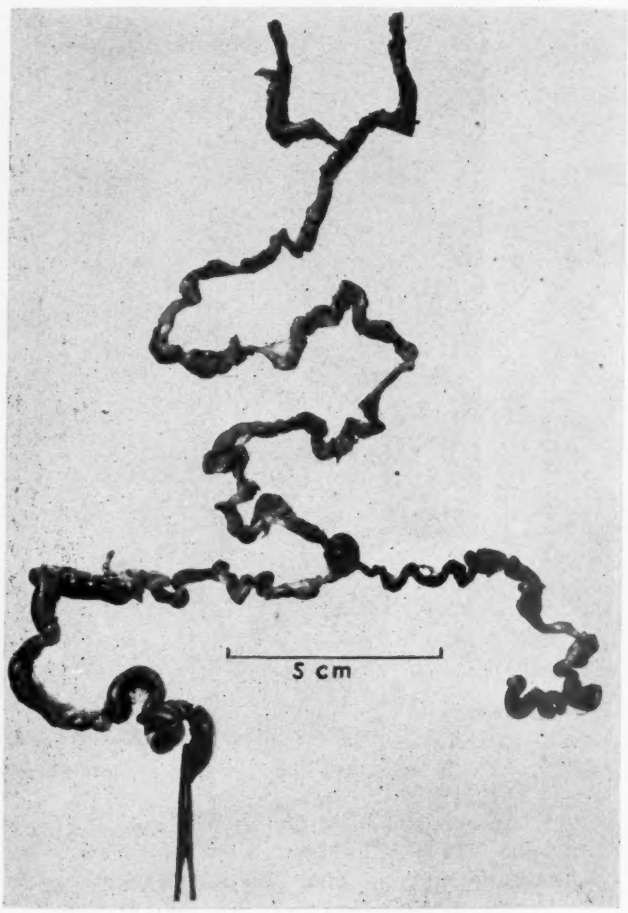

Fig. 5.

Fig. 4.—Common heart with umbilical cord and hepatic veins. (Liver tissue is largely dissected away.)

Fig. 5.—Alimentary tracts showing stomachs, common tract, and large intestine. Note appendices and enlargement at point of separation.

Both twins were dependent on the oxygenated blood received through the umbilical vein which went to the liver on the side of fetus Two. Fetus One had opportunity to receive some of this blood through the capillary connections of the liver, through the foramen ovale, and through any mixing of blood in the large ventricle. The more powerful "left" ventricle evidently forced blood through the interventricular foramen into the "right" ventricle. From here it flowed through the pulmonary arteries to the lungs or into the aorta through the ductus arteriosus.

Blood could reach the placenta by the umbilical arteries leading from fetus Two but drainage of used blood from One was less direct. This must have depended on mixing the blood in the heart and the passage of blood into the circulatory system of Two from the capillary beds of common tissue.

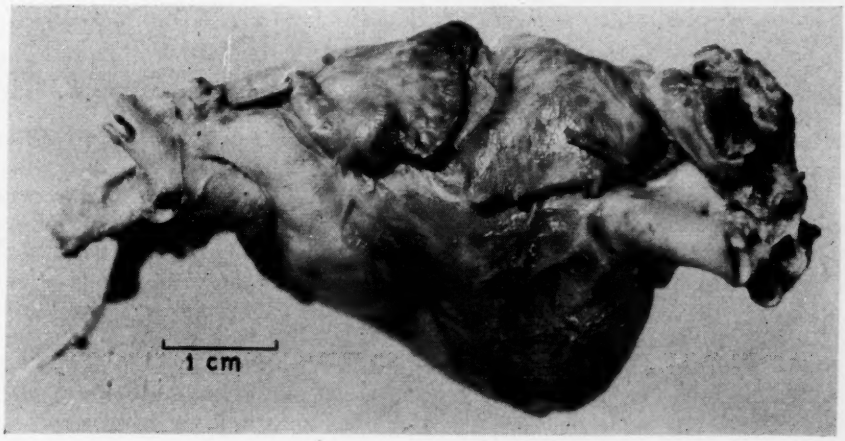

Fig. 6.—Common heart showing aortae, pulmonary artery, and some veins.

Discussion

Two noteworthy hypotheses have been made to explain the development of double monsters. Witschi has cited overripeness of the ovum as a potential cause. Stockard has demonstrated the production of monsters by arresting the development through cooling or through decreasing the oxygen supply.

In our case, the single member of the triplets differed in sex from the conjoined ones. The triplets must, therefore, have developed from two ova. The ova may have developed from the same or different ovaries. According to Arey, the human ovum is believed to be fertile for a period not much longer than one day. And as staleness advances, malformations are more frequent.

There could, however, have been a developmental arrest. The fertilized ovum which developed into the twins may have had an unfavorable descent or uterine implantation, having suffered an arrest through an oxygen deficiency.

Acknowledgments.—The author is indebted to Dr. H. E. Herman of the Corona Hospital for the conjoined fetuses, together with the clinical and delivery history; to Dr. E. Harold Shryock of the College of Medical Evangelists, for advice in examination of the specimen and criticism of the document; and to Dr. L. M. Ashley of the Micro-anatomy Department, for histologic examination; and to Mr. E. N. Hamilton of the Visual Education Department for photographic work.

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PREGNANCY FOLLOWING THE SMITHWICK OPERATION FOR HYPERTENSION*

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BECAUSE of the few women who have gone through pregnancy following the Smithwick operation, the addition of one who has delivered one baby prior to this operation and one afterward is instructive.

The Smithwick operation has not only removed certain individuals from that class unfortunately afflicted with hypertension and seemingly increased their longevity, but it would appear to have also given to some young women of this group the opportunity of bearing children with comparative safety.

Kellogg[1] reports ten such cases followed through eleven pregnancies. Blood pressure averaging 190/92 prior to operation, averaged 125/92 afterward and remained within normal limits throughout pregnancy in five cases; in these there was no albuminuria. Four showed moderate hypertension up to 160/90, and two had systolic pressures of 180. The pregnancy of one of the latter had to be interrupted at eight and one-half months. There were nine normal deliveries and two cesarean sections—one a repeat section and one done for a fulminating pre-eclampsia. Ten babies were born alive.

Newell and Smithwick[2] reported a study of fourteen cases with blood pressures averaging 196/130. Following operation and prior to the pregnancies the blood pressures averaged 135/87; only two had persistent albuminuria. The diagnosis of hypertension was as follows: essential hypertension 7; essential hypertension and associated pyelonephritis 2; two patients developed both during their first pregnancy; there were three cases of malignant hypertension with pyelonephritis in two of these. In nine cases the blood pressure remained within normal limits during pregnancy without albuminuria. In the other five there was little change in blood pressure until the third trimester; in one of these a 4 plus albuminuria necessitated interruption of the pregnancy at eight and one-half months.

Case Report

Mrs. B. presented a case of malignant essential hypertension with one pregnancy prior to and one subsequent to a Smithwick operation. She came to us first July 22, 1946, as a 26-year-old, married, white, gravida ii, who was approximately three months' pregnant. Her past medical history—Scarlet fever during childhood with no known sequellae; Smithwick operation in 1944 at the Crile Clinic for malignant essential hypertension evidenced by tinnitus, dizziness, severe headaches, and blood pressure which varied between 200 to 250 systolic and 150 to 190 diastolic of a year's duration. Following the operation the blood pressure was reduced to 90 to 120 systolic and 70 to 80 diastolic. On a check-up at Cleveland Clinic in February, 1946—"she seemed to be in excellent condition and renal function tests were all quite normal." Menstrual history—Normal twenty-five day cycle of five days' duration. Her last menstrual period was on April 14, 1946. Estimated date of confinement—Jan. 25, 1947. Marital history—Married five years. One previous pregnancy; latter part of 1942; pregnancy marked throughout entire course by severe nausea and vomiting; 8 pounds viable male delivered by family doctor at home by outlet forceps; no other data available. General history—essentially negative. History of present pregnancy—no complaints.

Physical Examination.—Revealed a short, well-developed, slightly obese white female. Her temperature, pulse, and respiration readings were normal. Eye grounds were normal.

*Presented at the regular meeting of the Pittsburgh Obstetrical and Gynecological Society, Jan. 12, 1948.

Heart and lungs were negative. Blood pressure was 138/90. Fundus 8 centimeters. Pelvic examination revealed a uterus approximately three months' pregnant. Pelvimetry was that of a gynecoid pelvis. Bilateral thoracolumbar incisional scars were noted.

Prenatal Laboratory Data.—X-ray of chest, intravenous urogram, urinalysis, phenolsulphonphthalein and Fishberg tests all gave normal readings; serology, complete blood count, blood sugar and nonprotein nitrogen were normal.

Prenatal Course.—A tendency toward excessive weight gain between the fourth and fifth months was controlled by restriction of salt, fluids, and diet; there was a 20-pound weight gain during the pregnancy. Urinalysis remained negative until early in the ninth month, when the patient developed a trace of albuminuria. This was accompanied by the appearance of nausea and frontal headaches. Her blood pressure, varying from 132/90 to 118/92, became elevated to 138/100 the last of the seventh month and rose to 140/110 at the beginning of the ninth month. In view of this picture of mild toxemia persisting in the face of adequate prenatal care, the patient was hospitalized for induction of labor.

Hospital Course.—Upon admission Dec. 28, 1946, the patient showed the following findings: blood pressure 136/82; fundus 28 cms.; right occipitoposterior position; head engaged; fetal heart sounds 140; cervix soft, two-thirds effaced, 1 to 2 cms. dilated, membranes intact. Urinalysis showed a trace of albumin.

Labor had not begun following a hot enema and 4 one minute doses of Pitocin, so the membranes were ruptured artificially. An hour later labor began with hard, regular uterine contractions, and at the end of six hours the head had descended in right occipitoposterior position to the low midpelvis, and the cervix had fully dilated. No further progress was evident following an hour and one-half of hard second stage contractions. Under ether anesthesia, following an unsuccessful attempt to rotate the head manually, Tucker-McLane forceps were applied and rotation and extraction of a well-developed, viable, 7 pounds 3 ounces female was performed with no difficulty. The placenta separated via Schultze-Ahlfeld, and a midline episiotomy was repaired.

Postpartum Course.—This period was marked by a persistent trace of albuminuria with a few red blood cells and white cells and an elevation of blood pressure developing on the fourth postpartum day, and varying from 178/112 to 140/100 at discharge on rest regime on the tenth postpartum day. A Fishberg test showed a concentration of 1.020 for the second and third specimens combined.

Follow-up Notes.—When seen at four, six, and ten weeks, and again at five and twelve months post partum, the patient had no complaints. Urine examination was normal. The blood pressure on the first two visits was 146/100 and 138/100. Thereafter it varied from 120/80 to 128/96. On check-up a year following delivery, her blood pressure was 108/92; complete blood count was normal; urine was negative; Fishberg 1.028, 1.029, 1.029; phenolsulphonphthalein was 75 per cent.

As far as treatment of these cases is concerned, judging from personal communications from R. S. Palmer, M.D., of Boston, James L. Poppin, M.D., of Lahey Clinic, J. A. LeFevre, M.D., of the Cleveland Clinic, and from our personal experience, the following should be instituted: (1) Drastic reduction of sodium ion and fat in the diet; (2) moderately high protein intake; (3) minimum weight gain; (4) adequate sedation; (5) sufficient rest; (6) interruption of pregnancy if toxemia appears.

Conclusion

It would seem that some of these hypertensive women may be allowed to attempt pregnancy. It should be remembered, however, that close supervision is necessary because the original hypertension may possibly be aggravated or pre-eclampsia may develop.

We wish to express our appreciation to Drs. Palmer, Poppin, and LeFevre for their communications.

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CONSERVATIVE TREATMENT OF PLACENTA ACCRETA WITH SUBSEQUENT NORMAL PREGNANCY

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IT IS generally accepted, and most textbooks recommend, that a retained placenta be removed surgically or manually. It is also generally believed that a placenta accreta or increta must be treated by hysterectomy.

Greenhill, in the ninth edition of DeLee-Greenhill, states that, in spite of fourteen reported cases where the placenta was allowed to remain and all the women survived, he believes that abdominal hysterectomy is the treatment of choice.

The following is a case report of placenta accreta or increta that was treated conservatively with no harmful effects. One year subsequently the patient had a normal delivery with a normal third stage.

D. M., aged 31 years, who had been under treatment for infertility, was examined on June 11, 1946. Her last normal menses was April 5, 1946, but she reported having had a scant one-day period on May 10, and another on June 1. Examination at this time revealed a slightly enlarged, soft uterus with a known previously existing cystic tumor in the right adnexa. A presumptive diagnosis of pregnancy was made.

She was not seen again until August 16, 1946, because she had not kept her scheduled appointment, nor made a new one. She came in at this time because of lower abdominal cramps and slight bleeding, both of a week's duration. Examination revealed a uterus the approximate size of a four months' pregnancy. The cervix was effaced, dilated 2 cm., and the amniotic sac was visible. She was sent directly to the hospital and treated with absolute bed rest, sedation, and progesterone. Twenty-four hours later, she was delivered of a 22 cm. fetus that showed no gross abnormalities. All efforts to express the placenta failed. Since there was very little bleeding, she was returned to bed and put on an Ergotrate regime. The next morning she was taken to the operating room where, under deep anesthesia, an attempt was made to remove the placenta manually. Palpation of the uterine cavity by both the operator and his assistant revealed no line of cleavage of the placenta. It was impossible to determine where the placenta ended and the uterine wall began. Because there was practically no bleeding, it was decided to follow a conservative course, and the patient again was returned to bed. She was kept in the hospital one week under treatment with Ergotrate, penicillin, and sulfadiazine. No serious bleeding nor evidence of infection developed so she was transferred home. She remained in bed at home for three weeks, during which time the uterus drained a bloody purulent lochia. Her only complaint was of cramps and pains in the legs, especially at night. Two weeks after the delivery, the fundus was not palpable abdominally. From the fourth to eighth week post partum the uterine drainage was of a bright bloody character and very moderate in amount. All discharge stopped on October 10, 1946. On the 19th of October the uterus was found to be of normal size, anterior, firm, and mobile. The right adnexal mass was still present.

She had a one-day menses on November 7, and a scant three-day period on December 15. On February 1, 1947, a presumptive diagnosis of six weeks' pregnancy was made and treatment for habitual abortion instituted. Her pregnancy was essentially normal throughout and she was delivered of a normal 7-pound infant on September 24, 1947, after an eleven-hour labor. A grossly normal placenta was delivered two minutes later by simple expression. Postpartum bleeding and the entire puerperium were normal.

It may be concluded from this case that placenta accreta, in the absence of unusual bleeding, can be treated conservatively without risk and that subsequent pregnancy may be entirely normal.

1007 MEDICO-DENTAL BUILDING

A REPORT OF EIGHTY CASES OF BENIGN SOLID TUMORS OF THE OVARY WITH SPECIAL REFERENCE TO COMPLICATIONS*

JULIUS A. FINO, M.D., WARREN, PA.

(From the Department of Gynecology, School of Medicine, University of Pittsburgh, Pittsburgh, Pa.)

AMONG the combined total of 24,951 gynecologic admissions at the Elizabeth Steel Magee Hospital and the St. Francis Hospital, there have been 80 cases of benign solid tumors of the ovary. Within the period of time involved, sixteen years at the Magee Hospital and nine years at the St. Francis Hospital, 7,780 specimens of ovarian tissue were submitted for pathologic diagnosis. Hence, the incidence of benign solid tumors of the ovary was 1.03 per cent.

The various types of benign solid tumors of the ovary included:

A. 73 fibromas
B. 1 myxofibroma
C. 1 adenofibroma
D. 1 neurofibroma
E. 1 leiomyoma
F. 3 Brenner tumors

The majority of these tumors were removed secondarily to other pelvic surgery. Complications due to a benign solid tumor of the ovary consisted of gross ascites and torsion with necrosis. The diagnosis of pelvic malignancy was suspected preoperatively in three cases because of ascites, loss in weight, and a large palpable pelvic mass, but these were proved to be benign.

Simple Fibroma of Ovary.—In the 73 cases of fibroma of the ovary, the diameter of the tumor varied from 1 cm. to 20 cm. Of these, 34 cases were associated with uterine fibroids, an incidence of 43.5 per cent. Gross ascites was preoperatively diagnosed in three cases in which the tumor size varied from 5 cm. to 15 cm. Fluid varying from 100 c.c. to 500 c.c. was found at the time of operation in 10 additional patients. The smallest tumor associated with fluid was 1 cm. in diameter.

It was of interest to note that all three patients in whom gross ascites was present showed one of the following pathologic changes in the ovary: large hemorrhagic infarct, gross necrosis, liquefaction necrosis, or degeneration with calcification. Eight other patients showed some form of degeneration and six of these had some ascitic fluid in the abdomen.

A preoperative diagnosis of adenocarcinoma of the ovary was made in one of the three patients with gross ascites. She was a 64-year-old woman admitted with a history of progressive loss in weight, "sudden" ascites, and pain in the abdomen. At operation, a pedunculated fibroma 12 cm. in diameter with partial torsion and necrosis was found. Approximately 3,000 c.c. of blood-tinged fluid was removed from the abdomen. The second patient was a 46-year-old woman admitted with a preoperative diagnosis of granulosa-cell tumor and uterine fibroids. A fibroma of the ovary, 8 cm. in diameter, associated with large pedunculated fibroids was found. There were approximately 1,500 to 2,000 c.c. of plasma-like fluid removed from the abdomen. The third patient was admitted with a preoperative diagnosis of ovarian cyst and uterine fibroids. She was 46 years old and her complaint was irregular,

*Presented at a meeting of the Pittsburgh Obstetrical and Gynecological Society, Oct. 6, 1947.

profuse vaginal bleeding. At operation, a fibroma 5 cm. in diameter associated with small uterine fibroids was removed. There were approximately 2,000 c.c. of straw-colored fluid present.

Myxofibroma of Ovary.—A 47-year-old patient was admitted with a preoperative diagnosis of large uterine fibroids. She had complained of left-sided pain for 10 years and gradual enlargement of the abdomen for 3 years; ascites was detected preoperatively. At operation, a tumor of the ovary was removed measuring 12 cm. by 15 cm. by 11 cm. There was considerable necrosis present. Approximately 2,000 c.c. of straw-colored fluid was removed from the abdomen at the time of operation.

Adenofibroma.—There was one case of an adenofibroma associated with endometriosis of the ovary. The history was that associated with pelvic endometriosis and on pelvic examination an enlarged, painful ovary was palpable. At operation it was noted that the ovary was not adherent and measured 7 cm. by 5 cm. by 4 cm. The remaining pelvic viscera appeared grossly normal and there was no ascites noted.

Neurofibroma.—A neurofibroma 4 cm. in diameter was removed secondarily to an acute ulcerative appendicitis in one case. The ovary was removed only because of its accessibility and also the possibility that it might have caused the patient trouble at a later date.

Leiomyoma of Ovary.—A diagnosis of leiomyoma of the ovary with liquefaction necrosis and cyst formation associated with gross ascites was made in one patient in whom a probable ovarian malignancy was considered preoperatively because of lower abdominal pain, gradual enlargement of the abdomen, detectable ascites, and loss of weight. The diagnosis of a benign solid tumor of the ovary was established histologically.

Fibromas Associated with Abdominal Malignancy.—In one patient, aged 67 years, a preoperative diagnosis of cystic ovaries and probable ovarian malignancy was made. At operation, a carcinoma of the right ovary measuring 5 cm. by 8 cm. by 8 cm. and a fibroma with degeneration measuring 4 cm. by 6 cm. by 4 cm. was found in the left ovary.

The second patient, aged 44 years, was admitted with a preoperative diagnosis of uterine fibroids. Her chief complaint was "mass in the abdomen" and "weight in the abdomen." At operation, a fibroma of the ovary with necrosis, measuirng 16 cm. by 10 cm. by 10 cm. was removed. There was also an adenocarcinoma of the cecum necessitating resection of the colon and a transverse ileocolostomy.

Torsion of an Adnexa Associated With a Benign Solid Tumor of the Ovary.—The tumors varied from 2 cm. to 7 cm. in diameter and this complication occurred in five patients. Gross ascites was found in one patient.

Brenner Tumors.—The three Brenner tumors included in this report were associated with uterine fibroids. The tumor size varied from 2 cm. to 6 cm. in diameter. Lower quadrant pain and tenderness on pelvic examination was found in all three cases. There was no associated ascites. A small fibroma in the contralateral ovary was found in one patient.

Discussion

The most outstanding complication associated with a benign solid tumor of the ovary in this series of cases was gross ascites. This occurred in five cases. The association of a large tumor mass in the pelvis with ascites accompanied with loss in weight accounted for the preoperative diagnosis of pelvic malignancy in three patients. Ascites associated with an abdominal tumor is most often associated with a malignancy, especially carcinoma of the ovary. One need only refer to the vastly accumulated literature to remind himself that this is not always true. This is well exemplified by a case not included in this report in which a preoperative diagnosis of malignant granulosa-cell tumor and uterine fibroids associated with gross ascites was made in a 41-year-old patient. At the time of operation, approximately 2,000 c.c. of ascitic fluid was removed. A large benign, posteriorly located fibroid was found which extended to the umbilicus and which had undergone considerable cystic degeneration.

While collecting material for this report, gross ascites was also noted in two patients with large degenerating theca-cell tumors. Fluid varying from 100 c.c. to 500 c.c., not detected preoperatively, was found in ten patients with a benign solid tumor of the ovary and six of these patients had degenerative changes within the tumor mass. All the cases with gross ascites had also degenerative changes present.

The benign solid tumors of the ovary were asymptomatic with the exception of those cases in whom complications occurred such as ascites, degeneration causing pain, or torsion of the adnexa.

All three Brenner tumors were removed because of a painful, enlarged mass in the adnexa with considerable associated tenderness on pelvic examination. The patients varied between the ages of 21 and 44 years.

The patients with simple fibromas, or one of the rarer forms of fibromas, varied between the ages of 19 and 67 years, but all tumor complications occurred in patients from 41 years to 67 years.

Meigs' syndrome (fibroma of ovary, ascites, and hydrothorax) was not present in any of the cases with gross or minimal ascites.

Granulosa cell tumors were not included in this report.

Summary

1. A report of 80 cases of benign solid tumors of the ovary is presented.

2. The incidence of benign solid tumors of the ovary is approximately 1 in 97 specimens of ovarian tissue.

3. The incidence of the various tumors based on the number of specimens of ovarian tissue submitted to the laboratory are:

1. Fibroma	1 in 106+ specimens of ovarian tissue
2. Leiomyoma of ovary	1 in 7,780
3. Myxofibroma of ovary	1 in 7,780
4. Adenofibroma	1 in 7,780
5. Neurofibroma	1 in 7,780
6. Brenner tumors	1 in 2,593+ specimens.

4. Ascites (gross or minimal) was the most common complication.

5. The presence of abdominal ascites with a pelvic tumor mass does not always mean malignancy.

6. The tumor mass causing the ascites may be a benign solid tumor of the ovary or a large degenerated uterine fibroid.

Note.—Appreciation is extended to Dr. B. Z. Cashman for his guidance in the preparation of this paper.

INTRAVENOUS VINBARBITAL SODIUM FOR OBSTETRIC ANALGESIA*

MATHIAS F. F. KOHL, M.D., PH.D., ROCKFORD, ILL.

(From The City Hospital of Akron)

THE use of intravenous vinbarbital sodium for the rapid relief of pain during the conduct of labor has been favorably reported.[1, 2] In approximately 150 cases, Lewis[2] gave an average intravenous dose of 15 grains vinbarbital sodium (range 5 to 25 grains) as the sole analgesic-anesthetic agent for the conduct of labor and delivery. About 60 per cent of his cases were delivered within thirty minutes of the initial injection and all cases were delivered within two hours. There was no interference with the progress of labor. Spontaneous delivery occurred in 33 per cent of primigravidas and 60 per cent of multigravidas. Respirations were spontaneous in 83 per cent of infants, while mild asphyxia, requiring no resuscitation, was present in another 13 per cent.

Intravenous vinbarbital sodium for combined analgesia-anesthesia was used by Lewis primarily in patients not seen or not requiring medication until delivery was imminent. It was the purpose of this study to extend the use of intravenous vinbarbital sodium to the earlier painful phases of the first stage of labor, as soon as uterine contractions are strong and productive of cervical dilatation. The requirements made upon an intravenous agent for relief of pain with a minimum of undesirable effects are more exacting under such a condition than when given at the last hour in large amounts to produce narcosis.

This study is an evaluation of 150 deliveries (68 primigravidas and 82 multigravidas) in which vinbarbital sodium was used intravenously in conjunction with intramuscular scopolamine hydrobromide. These are not consecutive cases, since experience, as will be shown, necessitated discontinuance in selected cases. The author has also been benefited by the experience of other members of the Obstetrical Service of The City Hospital of Akron who have similarly used vinbarbital sodium in well over 500 cases.

Criteria for Administration and Dosage Used.—An initial intravenous injection of 8 or 10 grains of vinbarbital sodium, depending on the size and weight of the patient, was given to primigravidas with strong four- to five-minute uterine contractions and cervical dilatation of 3 to 4 cm., and to multigravidas complaining with severe three-minute pains or with pains of lesser degree if cervical dilatation was 4 cm. The drug was given carefully over a two-minute period. Extravasation into the tissue caused painful tissue induration. Simultaneously, scopolamine hydrobromide $\frac{1}{150}$ grain (with 10 grains vinbarbital sodium) or $\frac{1}{200}$ grain (with 8 grains vinbarbital sodium) was given intramuscularly. If additional amounts of vinbarbital sodium were needed, it was repeated in half the initial dose, i.e., 4 or 5 grains. Delivery was conducted under cyclopropane anesthesia, for the most part, or ether anesthesia.

Types of Delivery.—In 150 cases (68 primigravidas, 82 multigravidas) delivery was effected as follows: low forceps, 120 cases; midforceps, 6 cases; breech

*Vinbarbital sodium is the nonproprietary name for sodium 5-ethyl 5-(1-methyl-1-butenyl) barbiturate and is distributed under the name of Delvinal Sodium. The material used in this study is a solution containing 1 grain per c.c. and was provided by the Medical Research Division of Sharp and Dohme, Inc.

extraction, 5 cases; extraperitoneal section, 1 case; and spontaneous, 18 cases. All midforceps were in primigravidas and all the spontaneous deliveries occurred in multigravidas.

Duration of Action and Effect Upon Labor.—The intravenous administration of 8 to 10 grains of vinbarbital sodium produces sleep within several minutes. This sleep is restless to varying degrees in half of patients. Bedside nurses are a necessity. Fifteen of the patients in this series (10 per cent) were so extremely restless and uncontrollable that constant nursing attention and restraint were necessary. Three of these patients fell out of bed when not watched.* Administration of additional vinbarbital sodium, unless carried to the point of anesthesia, is not the solution to the problem of the extremely restless patient. The answer is attention and restraint. In 135 cases, delivery occurred from thirty minutes to seven hours after the initial administration of the drug. The duration of good analgesia-amnesia was four to six hours. In ten cases, because of waning effect and increasing restlessness, the additional intravenous injection of half the initial dose was needed to carry the patient through to delivery. In four cases, the administration of vinbarbital sodium was discontinued after one or two additional doses because of prolonged labor with slow progress in spite of seemingly adequate uterine contractions. The prolonged labor was in no way attributable to the medication. In one case, after the initial dose of 10 grains of drug with the patient in good labor, uterine contractions were practically arrested and fourteen hours later, with the uterus still refractory and the cervix incompletely dilated, an extraperitoneal section was done. The last five unsuccessful cases were in primigravidas with posterior positions. This type of failure was not limited to the author's cases. Consequently, after experience in these cases, vinbarbital sodium was not used in posterior positions entering into labor slowly, with contractions of only fair quality and with the cervix firm and poorly effaced.

Degree of Analgesia-Amnesia.—Complete relief of pain and complete amnesia were experienced by 122 patients. Faint or partial recall of events and pain were reported by twenty patients. This experience of pain and the recall of events were associated with that period four to six hours after the initial injection, when another injection was necessary or when delivery was so imminent that there was little point to additional medication. Orientation and poor relief of pain were encountered in three patients. Not included are the five patients who had the drug discontinued, although all had good results for the period of usage.

Period of Recovery Following Delivery.—Following delivery (under cyclopropane) patients would sleep deeply for four to twelve hours. This would, on occasion, cause alarm to the patient's relatives. While gradually waking to full consciousness, patients were frequently restless and would get out of bed unless watched. Upon waking, patients, for the most part, experienced drowsiness, vertigo, blurring of vision, and poor recall—of slight to marked degree—until twelve to thirty-six hours after delivery. This "hang-over" was only slightly objectionable to most, but three patients were adamant that they never be given the drug again.

Resuscitation of Infants.—In 149 viable infants, 119 breathed spontaneously. The time interval for clamping the cord, aspirating mucus and fluid from nose and mouth, and clearing the pharynx with a suction catheter was 3 minutes. Flagellation of the feet and buttocks and massage of the base of the spine were employed. If, after this interval, no voluntary respiratory movements were evident and if the infant was limp and deeply cyanotic, artificial resuscitation with

*A number of patients outside of this series, to whom scopolamine was not given showed little change in regard to restlessness.

an alternating positive-negative pressure machine was started. Experience dictated that procrastination was not in order. Primary mechanical resuscitation was necessary in the case of twenty-one infants, with the time required usually being two to five minutes. In nine infants responding normally and breathing regularly, a secondary respiratory depression occurred at intervals varying from five to thirty minutes after birth. Resuscitation in these cases took usually one to ten minutes depending upon how soon the depression was noticed. It was imperative to watch all infants closely, even though they were breathing normally, for the possible secondary respiratory failure. There were five infants requiring longer than ten minutes' resuscitation for the establishment of regular breathing, namely, 12, 15, 20, 23, 180 minutes. This last instance was an infant breathing normally after three minutes of resuscitation for respiratory delay at birth. Thirty minutes after birth, the infant was found in its crib for all practical purposes dead. Only heroic efforts by a well-trained anesthetist over a three-hour period salvaged this life.

*Effect on the Newborn.**—This is an important, although much neglected, aspect of any study having to do with obstetrical analgesia-anesthesia. Twenty-five infants were chosen at random from cases reported here and other cases of colleagues. In 12 cases, respiration had been spontaneous; in 9 cases, primary respiratory depression necessitated one to ten minutes' resuscitation; and in 4 cases, a secondary respiratory failure required four to ten minutes' resuscitation. In this group of 25 infants, 9 infants required stimulation and oxygen because of periods of apnea and cyanosis during the first twenty-four hours of life. This was not carried into the second day of life. The "vinbarbital" babies were inclined to be drowsy and sluggish, difficult to keep awake for feeding, limp, cold, and full of mucus. Of the 25 babies, 16 were so depressed the first day; 9, the second day; 3, the third day; 1, the fourth day. Breast feeding was very unsatisfactory. These babies all required extra nursing attention.

Fetal and Maternal Complications.—The three fetal deaths in this series (anencephalic monster, hydrocephalic monster with spina bifida, normal stillborn with prolapsed cord) were not attributable to the method of analgesia. There were three infants in this series, premature by gestation and weight, that breathed spontaneously and did well. There was one case of erythroblastosis fetalis (not on the basis of Rh). Maternal complications were the usual for any series of 150 cases. The three patients falling out of bed and the patients requiring section for arrested labor can be considered to have had complications attributable to vinbarbital sodium.

Indications for the Use of Vinbarbital Sodium.—From experience in these 150 cases and information gained from approximately 500 cases of colleagues, it is considered advisable to reserve the use of intravenous vinbarbital sodium as outlined in this study to multigravidas and those primigravidas in whom labor promises to be rapid, in so far as can be judged from the quality of uterine contraction, station of the presenting part, and condition of the cervix. Cases of pelvic contraction and malposition are necessarily excluded. Vinbarbital sodium is contraindicated in the presence of uterine inertia or cervical rigidity, despite the impression gained in many cases that relaxation of the tense, apprehensive patient by the drug facilitates cervical dilatation by the contracting uterus and that labor is seemingly accelerated.

Summary and Conclusions

One hundred and fifty deliveries are reported in which intravenous vinbarbital sodium, supplemented by intramuscular scopolamine hydrobromide,

*I am indebted to Dr. Ralph Wymer, Resident in Obstetrics and Gynecology, for this preliminary data.

was given for the control of pain during labor. The medication is most successful in cases delivering within four to six hours. Constant nursing attention is necessary because of restlessness. Complete analgesia-amnesia occurred in 85 per cent of patients. Artificial resuscitation was necessary in 20 per cent of infants for either primary respiratory delay or secondary respiratory depression. There was a high incidence of apnea and cyanosis in infants during the first day of life. Properly used and with constant attention to limitations, intravenous vinbarbital sodium is a valuable drug in the obstetrician's armamentarium for the relief of pain.

References

1. Evans, J. R.: Am. J. Obst. & Gynec. 47: 821, 1944.
2. Lewis, M. S.: Am. J. Obst. & Gynec. 51: 395, 1946.

Correspondence

The Meigs' Syndrome

To the Editor:

I have read with great interest the excellent report on the case of Meigs' Syndrome in the JOURNAL **53**: 1042, 1947, by Dr. Herbert J. Simon. He has illustrated beautifully the most important point in these types of cases; namely, that even though the patient's clinical condition appears to be very grave, removal of the offending tumor gives complete and lasting relief.

In reference to the case report of Millett and Shell which appeared in the *Am. J. M. Sc.* **209**: 327 (March), 1945, Dr. Simon takes us to task, stating that a multilocular pseudomucinous cystadenoma of the ovary should not be reported as a case of Meigs' syndrome and quotes Dr. Meigs as follows:

"I don't think that papillary tumors or any kind of tumor that is not of the solid variety should be considered as cases of Meigs' syndrome."

I am unable to square this statement with the following statement by Dr. Meigs to us prior to the publication of our case report; this statement appears as a footnote in our article and is as follows:

"Believing that, in general, eponymic names of diseases should be restricted closely to the conditions as described by the original author, we asked Dr. Meigs if he thought that the term was justified in this case, which is not a fibroma, as originally described by him. We may say that he thinks that it is justified, and that the various types of primary lesions should be considered, from this point of view in one group."

The question of the postoperative chest tap is, I believe, of no great importance at this time. The syndrome has been fixed as a clinical entity and, inasmuch as the fluid did not recur with the removal of the offending tumor after four years when the patient was last seen, I believe we can definitely state that cause and effect have been clearly established.

I do wish that more of these case reports could be published more often in those journals relating to internal medicine and cardiology, to familiarize the men in these fields with this syndrome, as they are usually the first to see these types of cases. It is curious that nowhere in any textbook relating to the above specialties does Meigs' syndrome appear as a point of differential diagnosis. Perhaps the obstetricians and gynecologists can be persuaded to send their reports to journals relating to medicine and cardiology so as to familiarize the men in these fields with the syndrome, so that the surgeons can be called in much earlier to obtain the dramatic reversal in the clinical status of the patient.

JOSEPH MILLETT, M.D.

501 FULTON AVENUE
HEMPSTEAD, N. Y.
MARCH 3, 1948

Reply by Dr. Simon

To the Editor:

I am grateful for the opportunity of answering Dr. Millett's letter.

First, I wish to thank Dr. Millett sincerely for his flattering remarks about my report. Second, I heartily concur with his suggestion that more of these cases be reported in journals of internal medicine and cardiology in order to familiarize our internist brothers with the existence of the entity. (Dr. Millett saw the wisdom of this before he published his report and accordingly it appears in the *American Journal of Medical Sciences.*)

In reply to the question brought up in Dr. Millett's letter as to Dr. Meigs' personal opinion of the desirability of cystic tumors being included in the category of Meigs' syn-

drome, I can only say that, in my published report, I have quoted from a letter which Dr. Meigs wrote me and which I have on file. I agree to a great extent with Dr. Millett's remarks about the postoperative chest taps. Nevertheless, it is true that his case and McFee's were the only ones that reported a postoperative thoracentesis and theirs were the only cases of cystadenomas. Finally, while it is obviously important that it be understood that benign cystic tumors can produce ascites and hydrothorax, nevertheless, when benign (though potentially malignant) cystic tumors are included in the category of Meigs' syndrome, there is a grave danger that the concept of its benignity will be lost. I believe, therefore, that by limiting cases of Meigs' syndrome to solid tumors, we thus preserve in the medical mind the indisputable lack of malignancy of the syndrome even though occasional cases of benign cystic tumors which produce ascites and hydrothorax must be excluded.

HERBERT J. SIMON, M.D.

P.S. Since writing the above, I have read Samuel S. Rosenfeld's case report, "A Pseudomucinous Cyst of the Ovary With Ascites and Hydrothorax" in the *New York State Journal of Medicine,* of March 1, 1948. Dr. Rosenfeld told me that he did not have to do a postoperative chest tap on his patient. I call attention to this in spite of the fact that it weakens my position and strengthens Dr. Millett's. H. J. S.

20 EAST 76TH. STREET
NEW YORK.
APRIL 30, 1948

Items

American Board of Obstetrics and Gynecology

The next scheduled examination (Part I) written examination and review of case histories, for all candidates, will be held in various cities of the United States and Canada on Friday, February 4, 1949. New Applications may be made until November 1, 1948. Application forms and Bulletins are sent upon request made to

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY, INC.,
1015 Highland Building,
Pittsburgh 6, Pennsylvania.

Prize Award

The South Atlantic Association of Obstetricians and Gynecologists announces the establishment of "The Foundation Prize." Authors of papers on obstetrical or gynecological subjects desiring to compete for the prize may obtain information from Dr. E. D. Colvin, Secretary-Treasurer, 1259 Clifton Road, N. E., Atlanta, Ga.

Erratum

In the article by Joseph A. Kurcz and Mahlon S. Sharp, entitled "Congenital Absence of One Ovary Associated With Contralateral Tubal Pregnancy," in the June issue of the JOURNAL, on page 1065, the Woman's Hospital, from which the article was written, should have been followed by the address, Detroit, Michigan.

Dr. Sharp's present address is 512 Olds Tower Building, Lansing, Mich.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

American Gynecological Society. (1876) *President,* Ludwig Emge. *Secretary,* Norman Miller, Ann Arbor, Mich. Next meeting, May, 1949, Hot Springs, Va.

American Association of Obstetricians, Gynecologists and Abdominal Surgeons. (1888) *President,* James R. Bloss, Huntington, W. Va. *Secretary,* Leroy A. Calkins, 418 11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 7-9, 1949.

Central Association of Obstetricians and Gynecologists. (1929) *President,* Earl C. Sage, Omaha, Neb. *Secretary-Treasurer,* John I. Brewer, 104 South Michigan Ave., Chicago, Ill. Annual meeting Louisville, Ky., Oct. 23, 24, and 25, 1947.

South Atlantic Association of Obstetricians and Gynecologists. (1938) *President,* S. R. Norris, Jacksonville, Fla. *Secretary,* E. D. Colvin, 1259 Clifton Road, N.E., Atlanta, Ga. Annual meeting at Williamsburg, Va., February 10 to 12, 1949, at the Williamsburg Inn and Lodge.

A. M. A. Section on Obstetrics and Gynecology. *Chairman,* William F. Mengert, Dallas, Texas. *Secretary,* A. B. Hunt, Mayo Clinic, Rochester, Minn. Annual meeting June, 1947.

New York Obstetrical Society. (1863) *President,* Albert H. Aldridge. *Secretary,* Claude E. Heaton, 205 East 69th St., New York 21, N. Y. Second Tuesday, from October to May, Yale Club.

Obstetrical Society of Philadelphia. (1868) *President,* Carl Bachman. *Secretary,* George A. Hahn, 255 S. 17th St., Philadelphia, Pa. First Thursday, from October to May.

Chicago Gynecological Society. (1878) *President,* Herbert E. Schmitz. *Secretary,* Edward M. Dorr, 30 N. Michigan Ave., Chicago 2, Ill. Third Friday, from October to June, Hotel Knickerbocker.

Brooklyn Gynecological Society. (1890) *President,* Alexander E. Dunbar. *Secretary,* William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.

Baltimore Obstetrical and Gynecological Society. (1929) *President,* Lawrence Wharton. *Secretary-Treasurer,* John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.

Cincinnati Obstetrical Society. (1876) *President,* Stanley T. Garber. *Secretary,* Joseph G. Crotty, 146 West McMillan St., Cincinnati, Ohio. Third Thursday of each month.

Louisville Obstetrical and Gynecological Society. *President,* Rudy F. Vogt. *Secretary-Treasurer,* Glenn W. Bryant, Louisville, Ky. Meetings fourth Monday of each month from September to May, Brown Hotel.

Portland Society of Obstetrics and Gynecology. *President,* Ronald Frazier. *Secretary-Treasurer,* Gifford D. Seitz, 919 Taylor St. Bldg., Portland 5, Ore. Meetings last Wednesday of each month.

Pittsburgh Obstetrical and Gynecological Society. (1934) *President,* James Hodgkiss. *Secretary,* Clarence H. Ingram, Jr., 902 Peoples East End Building, Pittsburgh 6, Pa. First Monday of October, November, December, January, February, March, April, and May.

Obstetrical Society of Boston. (1861) *President,* Paul Gustafson. *Secretary,* H. Bristol Nelson, 1180 Beacon Street, Brookline, Mass. Third Tuesday, October to April, Harvard Club.

New England Obstetrical and Gynecological Society. (1929) *President,* Arthur E. G. Edgelow, Springfield, Mass. *Recorder,* Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and December.

Pacific Coast Obstetrical and Gynecological Society. (1931) *President,* Henry N. Shaw. *Secretary-Treasurer,* William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif. Next meeting in Seattle, Wash., Oct. 1 to 4, 1947.

Washington Gynecological Society. (1933) *President,* William J. Cusack. *Secretary,* John Parks, 901 23 St., N.W., Washington, D. C. Fourth Saturday, October, November, January, March, May.

New Orleans Obstetrical and Gynecological Society. (1924) *President,* Woodard D. Beacham. *Secretary,* Harry Meyer, 3439 Prytania St., New Orleans, La. Meetings held October, November, January, March, and May.

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*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

St. Louis Gynecological Society. (1924) *President,* Joseph A. Hardy, Jr. *Secretary,* Paul F. Fletcher, 634 North Grand Ave., St. Louis 3, Mo. Meetings second Thursday, October, December, February, and April.

San Francisco Gynecological Society. (1929) *President,* Albert M. Vollmer. *Secretary,* Daniel G. Morton, University of California Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.

Texas Association of Obstetricians and Gynecologists. (1930) *President,* Warren E. Massey. *Secretary,* George F. Adam, 4115 Fannin St., Houston 4, Tex.

Michigan Society of Obstetricians and Gynecologists. (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President,* O. W. Picard. *Secretary,* Carl F. Shelton, 910 David Broderick Tower, Detroit 26, Mich. Meetings first Tuesday of each month from October to May (inclusive).

Central New York Association of Obstetricians and Gynecologists. (1938) *President,* Raymond J. Pieri. *Secretary,* Nathan N. Cohen, 713 E. Genesse St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.

Alabama Association of Obstetricians and Gynecologists. *President,* Gilbert F. Douglas. *Secretary,* Hunter Brown, 1922 South Tenth Ave., Birmingham, Ala.

San Antonio Obstetric Society. *President,* I. T. Cutter. *Secretary,* S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.

Seattle Gynecological Society. (1941) *President,* Donald J. Thorp. *Secretary-Treasurer,* Charles D. Kimball, 734 Broadway, Seattle 22, Wash. Meetings held on third Wednesday of each month, Washington Athletic Club.

Denver Gynecological and Obstetrical Society. (1942) *Secretary,* Warren W. Tucker, 1820 Gilpin St., Denver 6, Colo.

Wisconsin Society of Obstetrics and Gynecology. (1940) *President,* Henry A. Sincock. *Secretary-Treasurer,* Edith McCann, 425 East Wisconsin Ave., Milwaukee 2. Meetings held in May and October.

San Diego Gynecological Society. (1937) *President,* R. C. Hall. *Secretary,* D. Dalton Deeds, 2001 Fourth Ave., San Diego, Calif. Meetings held on the last Wednesday of each month.

North Dakota Society of Obstetrics and Gynecology. (1938) *President,* Ralph E. Leigh, Grand Forks. *Secretary,* G. Wilson Hunter, 807 Broadway, Fargo, N. D.

Virginia Obstetrical and Gynecological Society. (1936) *President,* John Boyd. *Secretary-Treasurer,* William Durwood Suggs, Monument Ave. and Lombardy St., Richmond, Va. Next meeting not announced.

Columbus Obstetric and Gynecologic Society. (1944) *President,* Dana Cox. *Secretary,* Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held fourth Wednesday of each month.

Naussau Obstetrical Society. (1944) *President,* Robert S. Millen. *Secretary-Treasurer,* Peter La Mariana, Williston Park, L. I., N. Y. Meetings, bimonthly from October to May.

Bronx Gynecological and Obstetrical Society. (1924) *President,* H. J. Lesnick. *Secretary,* Mark Daniel, 2344 Davidson Ave., Bronx 53, N. Y. Meetings, fourth Monday monthly from October to May.

Washington State Obstetrical Society. (1936) *President,* John H. Fiorino, Everett. *Secretary,* H. H. Skinner, Yakima, Meetings, first Saturday of April and October.

Kansas City Obstetrical and Gynecological Society. (1922) *President,* Joseph G. Webster. *Secretary,* William C. Mixson, 320 W. 47th St., Kansas City, Mo. Meetings, last Thursday, September, November, January, and March; first Thursday, May, University Club.

Los Angeles Obstetrical and Gynecological Society. (1914) *President,* Carl E. Krugmeier. *Secretary-Treasurer,* A. M. McCausland, 3780 Wilshire Blvd., Los Angeles, Calif.

North Carolina Obstetrical and Gynecological Society. (1932) *President,* Wallace B. Bradford. *Secretary,* Richard B. Dunn. Meetings semiannually.

The Society of Obstetricians and Gynecologists of Canada. (1944) *President,* William A. Scott. *Secretary,* James Goodwin, 516 Medical Arts Bldg., Toronto, 5. Meetings held annually, date of next meeting to be announced later.

Akron Obstetrical and Gynecological Society. (1946) *President,* S. B. Conger. *Secretary-Treasurer,* Alven M. Weil, 1030 First National Tower, Akron 8, Ohio. Meetings held third Friday of January, April, July, and October, City Club of Akron, Ohio, Bldg.

Minnesota Society of Obstetrics and Gynecology. *President,* Everett C. Hartley. *Secretary,* John Haugen, 100 E. Franklin Ave., Minneapolis, Minn. Meetings held spring and fall.

Miami Obstetrical and Gynecological Society. (1946) *President,* M. C. Wilson. *Secretary,* George A. Mitchell, Huntington Bldg. Meetings, second Thursday in January, March, May, and November.

Omaha Obstetrical and Gynecological Society. (1947) *President,* Charles F. Moon. *Secretary,* Donald C. Vroman, 813 Medical Arts Bldg., Omaha 2, Neb. Meetings held third Wednesday in January, March, May, September, November.